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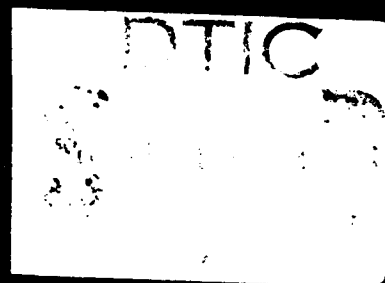NATIONAL BUREAU OF STANDARDS-1963-A

DEVELOPMENT OF BIODEGRADABLE DENTALS
PROSTHESIS IN MAXILLOFACIAL SURGERY

Annual Technical Report
Years Second and Third

U.S. ARMY INSTITUTE OF DENTAL RESEARCH
U.S. ARMY MEDICAL RESEARCH AND
DEVELOPMENT COMMAND

Contract DAMD17-78-C-8059

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SOUTHERN RESEARCH INSTITUTE

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DEVELOPMENT OF BIODEGRADABLE IMPLANTS
FOR USE IN MAXILLOFACIAL SURGERY

ANNUAL REPORT

Danny H. Lewis, Richard L. Dunn, Robert A. Casper

October 1981

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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)* Biodegradable polymers were synthesized and fabricated into fracture-fixation plates for use in the management of maxillofacial injuries. The plates, however, did not possess sufficient strength and rigidity for properly immobilizing the healing bone. The biodegradable resins were subsequently reinforced with both ceramic and carbon fibers by a lamination process. The resulting appliances were not totally biodegradable, but served as a model study for methods
(continued on next page)

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to obtain the desired composite material properties. In vitro experiments with these materials showed that the composites were capable of retaining sufficient strength and integrity, in a pseudo-physiological environment, throughout the period normally required for formation of primary ossious union and subsequent healing. Implantation in dogs, conducted by the U. S. Army Institute of Dental Research, demonstrated the suitability of the fiber-reinforced resin systems for use in the promotion of healing in mandibular defects. Both biodegradable fibers and crosslinkable biodegradable resins were examined as met   for obtaining a totally biodegradable fixation system.

DEVELOPMENT OF BIODEGRADABLE IMPLANTS
FOR USE IN MAXILLOFACIAL SURGERY

Annual Technical Report
Years Two and Three

to

U.S. ARMY INSTITUTE OF DENTAL RESEARCH
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                                       SOUTHERN RESEARCH INSTITUTE

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I. SUMMARY

This report covers work conducted during the second and third contract years on Project 4150, Contract DAMD17-78-C-8059, "Development of Biodegradable Implants for Use in Maxillofacial Surgery." The objective of the project is to develop high-strength resorbable materials useful in the treatment of maxillofacial injuries. To meet this objective, we prepared high-purity monomers, synthesized high-molecular-weight polymers, fabricated test specimens, investigated various model reinforcement schemes using nonbiodegradable fibers, and examined biodegradable hydroxylapatite and potentially crosslinkable copolyoxalate systems for the production of totally biodegradable fixation plates.

Monomers of high purity were prepared by numerous re-crystallizations, and their purities were ascertained by differential scanning calorimetry. These monomers were used to prepare high-molecular-weight polymers and copolymers of DL-lactide, L-lactide, and glycolide which were then used in the fabrication of reinforced and non-reinforced polymeric bone fixation plates for evaluation of flexural properties and suitability as fixation appliances.

In studies conducted during the past two years, orientation of biodegradable polymers, alone, was proven to be insufficient for producing materials with the required mechanical properties. However, when both ceramic and carbon fibers, available from commercial sources, were laminated into bio-degradable resins as a model system, these composite materials had sufficient strength and rigidity for use in bone fixation and repair. In vitro experiments with these materials showed that the composites were capable of retaining sufficient strength and integrity, in a pseudo-physiological environment, throughout the period normally required for formation of primary ossious union and subsequent healing. Implantation in dogs, conducted by the USAIDR, demonstrated the patency of the fiber-reinforced resin systems in the promotion of healing in mandibular defects.

For the attainment of totally biodegradable fracture-fixation systems, both the incorporation of biodegradable ceramic fibers into existing polylactide resins and the use

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of crosslinkable biodegradable resins are viable methods, and our current efforts have been directed toward the development of these materials. Both approaches require further work to achieve a totally biodegradable fixation system with subsequent in vitro and in vivo studies to determine the rate of biodegradation and the retention of desirable mechanical properties.

II. INTRODUCTION

The need for improved methods and materials for the management of severe maxillofacial wounds is well recognized in view of the substantial portion of these in recent conflicts. In its investigations of various approaches to improved surgical methods and patient care, the Army Institute of Dental Research has constantly sought better materials for repair of jaw fractures.

Bone consists of a framework of collagenous fibers, a mineral matrix, which is primarily calcium hydroxylapatite, and a small amount of polysaccharides. Even though a large portion of the volume of bone is water, bones are hard and tough. Although varying considerably in properties depending on function, bones commonly have tensile strengths of 6,000 to 20,000 psi and values of modulus of elasticity of 1 to 3×10^6 psi. Metals are stronger and stiffer than bone. Most polymeric materials are as strong as bone but more deformable, and require fiber reinforcement or crosslinking to equal the stiffness characteristic of bone.

Fracture fixation in maxillofacial surgery has traditionally been accomplished by the use of rigid metallic fixation plates or cribs with metal bone screws used to attach the appliance to the surrounding bone. This method of fixation is less than satisfactory for two reasons: (1) rigid fixation devices, which are of primary importance in the promotion of initial fracture union, may cause cortical bone to atrophy as the healing process progresses and (2) additional surgical procedures are required for removal after healing is complete, thus increasing surgical cost and patient inconvenience.

Ideally, fixation appliances should vary in stiffness as healing progresses, transferring an increasing proportion of the mastication forces to the mandibular bone as it becomes further ossified. This progressive load transfer assures that the forming bone is strained and exercised. Both processes are necessary for the formation of healthy hard tissue whose properties are commensurate with those of virgin bone. The development of a variable-stiffness fixation device is best achieved by a degradable polymer system whose degradation products are non-toxic and harmless to the host. A biodegradable material with properly tailored physical properties and degradation kinetics would ensure the development of strong, healthy bone and would eliminate the need for surgical removal of the fixation device on completion of the healing process.

At this time, two routes are available for achieving a totally biodegradable fracture-fixation system. One route

consists of the fabrication of a biodegradable reinforcement material for PLA, and we are currently pursuing hydroxylapatite ceramic materials as candidates for this application. The other method centers on the chemical crosslinking of a biodegradable polymer system. Our efforts with PLA in this area have not been rewarding, and we are now concentrating on copolyoxalate systems.

The sections which follow describe the research carried out on Contract DAMD17-78-C-8059 from August 1, 1979, to August 21, 1981.

III. MONOMER AND POLYMER PREPARATION

A. Monomer Preparation

The first and perhaps most crucial step in any polymer-development program directed toward improving properties is the preparation of high-purity monomers. This is especially true for biodegradable polymers of lactic and glycolic acids.

1. DL-Lactide

The DL-lactide, as received from Clinton Corn Processing Company of Clinton, Iowa, is impure; its melting point is usually 113°C. To 6.0 kg of crude DL-lactide was added 12 liters of isopropanol, and the mixture was heated to the boiling point until all the lactide dissolved. Heating was discontinued, and the mixture was allowed to cool slowly to room temperature. The mixture was cooled to 5°C, and the crystallized lactide was isolated by inverted filtration. In the next recrystallization, one part of lactide was added to six parts of benzene, and 3.0 g of activated charcoal was added. The mixture was heated to reflux and filtered while hot through a sintered glass funnel containing a bed of glass wool. The mixture was then heated to the boiling point again, and two parts benzene were removed by distillation to azeotrope out residual water. The solution was allowed to cool to room temperature. The crystalline lactide was isolated by filtration and protected from atmospheric moisture with a rubber dam during the filtration. The recrystallization from benzene was repeated twice more, without charcoal, and the lactide was dried in a vacuum oven at 50°C. The total recovery of purified lactide was 2.6 kg, and the monomer had a melting point of 126-127.5°C.

2. L-Lactide

L-Lactide may be purified by the following procedure. The material as received is dried in vacuo at room temperature for 24 hours. The crystals are then transferred to a round-bottom flask, and ethyl acetate is added in the ratio of 1 mL of ethyl acetate per 2 grams of lactide. The mixture is then brought to reflux for several hours until all the lactide is dissolved and the solution is allowed to cool overnight. Crystallization is enhanced by packing the flask in ice for several hours. The crystals are then collected, and the recrystallization procedure is repeated a minimum of three more times. At the end of the last recrystallization cycle, the crystals are collected and dried in vacuo for 24 hours.

All handling of the L-lactide crystals is conducted in a nitrogen-filled glove box under nitrogen purge. All glassware is oven dried at 150°C for 24 hours, and assembly is carried out inside the dry box.

3. Glycolide

Glycolide monomer was prepared and purified by the following method. In a three-neck flask equipped with a thermometer, a distillation head, and a condenser was added 6 kg of a 65% aqueous solution of glycolic acid (Ashland Chemicals). The mixture was heated to boiling, and the water was distilled off. When the water ceased to distill, the system was placed under a water-aspirator vacuum, and the mixture was maintained below 180°C until the reaction water was completely removed. The resulting molten low-molecular-weight polyglycolide was slowly poured into stirred isopropanol at 5°C, and the prilled material was collected as a light brown solid on a Buchner funnel. The polymer was dried in a vacuum oven at room temperature for 24 hours.

The low-molecular-weight polyglycolide was separated into smaller portions and thermally cracked to form glycolide. To 1 kg of polymer in a three-neck flask, connected to two additional flasks utilized as receivers for the glycolide, was added 10 g of antimony(III) oxide catalyst. The pressure of the system was reduced to about 3 mm, and the temperature was raised to about 270°C over 8 hours. The crude glycolide distilled as it formed and was collected as a solid in the traps, which were cooled with dry ice and acetone. The light yellow distillate was melted and poured slowly into isopropanol at 5°C, and the prilled glycolide was collected by filtration and protected from atmospheric moisture with a rubber dam during isolation. The yield of glycolide was 920 g (92%).

Several portions of prilled glycolide were combined and recrystallized twice from dry ethyl acetate. The purified monomer was dried in vacuo in a desiccator heated to 60°C. The melting point of the purified glycolide was 79-80.5°C.

B. Polymer Synthesis

1. Poly(DL-lactide) (PLA)

The following procedure is representative of that used in the preparation of a typical batch of poly(DL-lactide). In a dry, 2000-mL, three-neck flask equipped with a mechanical stirrer and a nitrogen inlet was placed 1500 g of DL-lactide, 15 drops of lauryl alcohol, and 0.3 g (0.02%) of tetraphenyltin. The loading of the reaction vessel was carried out in a nitrogen-filled glove box. The flask was removed from the dry box, connected to a nitrogen line, and placed in an oil bath preheated to 170°C and stirred for 3 hours. Stirring was then

discontinued, and heating was continued for an additional 18 hours. The polymer was allowed to cool to room temperature, and then it was frozen in a dry-ice bath. The flask was broken, and the frozen polymer was removed and dissolved in methylene chloride. The viscous solution was poured slowly into stirred methanol, and the precipitated polymer was collected and dried in vacuo at 50°C.

2. Poly(L-lactide) (L-PLA)

L-PLA was prepared in our laboratories by a procedure similar to that used for polymerizing DL-lactide. L-lactide, freshly recrystallized from benzene, was dried in vacuo for 24 hours. Oven-dried (150°C, 24 hours) glassware was assembled in an atmosphere of nitrogen. Tetraphenyltin (0.029%) and lauryl alcohol (1 drop from a standard Pasteur pipette) were added to 100 grams of the heated lactide. Heating was then continued at 170°C for 18 hours, and stirring was continued until the polymer became too viscous to stir, usually four to six hours. During the polymerization process, the contents of the reactor vessel were kept under a nitrogen (ultrapure) atmosphere. After the polymer was cooled, it was dissolved in dichloromethane and reprecipitated into methanol to remove traces of monomer and low-molecular-weight fractions. After it was dried overnight in vacuo to remove the methanol, the inherent viscosity of the polymer was determined in chloroform. For the upper limit, typical values of 1.5-2.0 dL/g were obtained.

C. Copolymer Synthesis

One method of controlling the biodegradation rate of the bone-plate materials is to use copolymers of lactide and gly-colide. The copolymers with the higher glycolide content tend to degrade faster in vivo. We proposed to prepare laminates from copolymers of 75/25 DL-lactide/glycolide and copolymers of 50/50 DL-lactide/glycolide. Polymers with glycolide are very difficult to prepare in high molecular weights unless the glycolide is quite pure and the proper catalyst is used. To test the glycolide purity as well as our polymerization conditions, we prepared about 100 g of a 75/25 DL-lactide/glycolide copolymer. We employed the same catalyst and reaction conditions as used in the preparation of poly(DL-lactide). The copolymer thus prepared had an inherent viscosity value, although it was less than that obtained for the poly(DL-lactide) homopolymer, still representative of a high-molecular-weight material.

Because of the slight decrease in viscosity with the 75/25 copolymer, a different catalyst was used for the preparation of the 50/50 copolymer of DL-lactide and glycolide. Rather than the tetraphenyltin and lauryl alcohol catalyst and initiator system used for polymerization of DL-lactide, we used antimony trifluoride as the catalyst without the addition of

a chain initiator. Antimony trifluoride is commonly employed as the catalyst for glycolide polymerizations. The 50/50 copolymer obtained from this polymerization had an inherent viscosity of 0.59 dL/g measured in chloroform at 30°C. However, the inherent viscosity was 1.02 dL/g measured at 30°C in hexafluoroisopropanol. As expected, the copolymer was not as soluble in chloroform as the poly(DL-lactide) homopolymer, and polyglycolide solvents such as hexafluoroisopropanol were required to obtain the proper chain extension in solution. The viscosity value of this copolymer as measured in the better solvent represents high-molecular-weight material suitable for lamination studies.

IV. FIBER-REINFORCED LAMINATES

Polymers of DL-lactide reinforced with carbon fibers gave the highest values of flexural strength of all materials that we studied in the first year of the program. From these studies, we concluded that high-modulus fibers incorporated into biodegradable polymers would provide the strength needed for bone-plate materials, especially as a model system to demonstrate feasibility of the concept. During the past two years of the contract, we continued the investigation of carbon fabrics and fibers as reinforcing agents. Commercially available ceramic fibers were investigated as well.

A. Preparation of Fiber-Reinforced Films

We prepared poly(DL-lactide) (PLA) films reinforced with both fabrics and yarns to determine the utility of the materials in the fabrication of fracture-fixation plates with improved flexural properties. We used fabrics of both carbon and ceramic fibers. The carbon fabric was produced by carbonization of a fabric of rayon yarns. The ceramic fabric contained 3M Company's Nextel 312 ceramic fibers. Non-reinforced PLA films were used to fabricate control samples.

Films of PLA were prepared from polymers having inherent viscosities of 0.58, 1.14, and 1.27 dL/g as measured in chloroform at 30°C. These viscosity values represent low- and medium-molecular-weight polymers. All of the PLA films were prepared by the following general procedure:

> Approximately 97 mL of a 13% solution of PLA in p-dioxane was injected into a 3 x 9 in. spin-casting cup rotating at 3600 rpm. The spin cup was lined with a sheet of Mylar® film to prevent the polymer from sticking to the cup. After the solvent had completely evaporated, the film was removed from the cup and dried at 60°C in vacuo for 12 to 24 hr to remove all traces of solvent. The stiff and brittle film was then placed in a hydraulic press at 70°C and 40,000 psi to remove the bubbles in the film caused by the evaporation of the solvent.

The procedure for the preparation of fabric-reinforced films was as follows:

> Approximately 30 mL of a 13% solution of PLA in p-dioxane was injected into a 3 x 9 in. spin-casting cup rotating at 3600 rpm. The spin cup was lined with a sheet of Mylar® film to prevent the polymer from sticking to the cup. When most of the solvent had evaporated, a sheet of the carbon or ceramic fabric cut to the same 3 x 9 in.-size was placed in the cup onto the tacky

PLA film. An additional 47 mL of the PLA
solution was injected into the rotating
cup, and the solvent was evaporated. Then
another 10 mL of the PLA solution was added
to the cup to yield a smoother surface of
PLA on the fabric. The cup was allowed to
spin until the film appeared to be free of
solvent. The film was removed from the
cup and dried at 60°C in vacuo for 12 to
24 hr to remove the last traces of solvent.
The stiff and brittle film was placed in
a hydraulic press at 70°C and approximately
25,000 psi to press out the bubbles caused
by the evaporation of the solvent.

The preparation of the fiber-reinforced films required a
different procedure from that used for the PLA and fabric-
reinforced films. We used both carbon and ceramic fibers. The
carbon fibers were Thornel 300 graphite yarns, produced by Union
Carbide from a pitch precursor, and Thornel 50 carbon yarns, pro-
duced by carbonization of polyacrylonitrile (PAN). The ceramic
fibers were Nextel AB 312 obtained from 3M Company and Fiber
FP developed by DuPont.

Initially, we attempted to prepare fiber-reinforced PLA
films by winding the continuous filament yarns around two
parallel posts which were six inches apart. The filament yarn was
wound around the two posts to form a continuous layer of yarn on
both sides. Each layer of fibers was then painted with several
coats of a solution of PLA in methylene chloride until the fibers
were encapsulated in the polymer. The wound film was cut free of
the posts, and the inside surface was coated with several layers
of PLA polymer. The film was then dried in vacuo to remove all
traces of solvent.

We found, however, that the sharp bends around the posts
caused excessive breakage of the high-modulus carbon and ceramic
fibers. We modified the procedure to circumvent this problem.
In place of the parallel posts, a plastic jar with a diameter
of 4.5 inches was used. The modified procedure was as follows:

The plastic jar was mounted on a manual winder
such that the yarn could be wound in a flat ribbon
onto the jar. A sheet of Mylar film was placed
on the surface of the jar to prevent polymer from
adhering to it. Then the carbon or ceramic yarn
was slowly wound around the circumference of the
jar onto the Mylar film. A solution of PLA in
p-dioxane was sprayed on the band of yarns from
an aerosol can containing the polymer solution
and Freon-12 propellant. Subsequent coats of PLA

were applied and dried until the exposed
side of the fibers was completely covered
with polymer. The thin film containing
fibers and polymer was removed from the
circumference of the jar, cut into seg-
ments, and placed in an oven at 70-85°C
for about two minutes to allow the cy-
lindrically curved films to flatten out.
The uncoated side of the fibers was then
painted with several coats of PLA until
the fibers were completely enclosed in
a polymer matrix. The fibrous film was
dried at 60°C in vacuo for 12 to 24 hours
to remove all traces of solvent, and
then it was placed in a press at 70°C
and 25,000 psi to remove the bubbles caused
by solvent evaporation.

B.   Laminate Preparation and Testing.

Test samples were prepared by cutting PLA and fiber- or
fabric-impregnated PLA films into 3 x 0.5-in. pieces and placing
them in alternate layers in a heated press at 65°C under pressure
until they completely fused to form a laminate structure.

The flexural properties of fiber-reinforced materials are
highly dependent upon the amount of fiber that is added to the
polymer. To determine the optimum level of carbon fabric needed
in the PLA composites, we prepared laminates which contained 43,
55, 57, and 67% of carbon. These laminates were fabricated by
varying the number of carbon layers and PLA layers used to form
the laminate.

The test results for fabric-reinforced samples are presented
in Table I. As evident from the data shown in Table I, the per-
centage of carbon in the laminate is critical in obtaining high
flexural properties. A value of 55% of carbon in the laminate
appears to be the optimum level for reinforcement. Too much
carbon fiber in the laminate shows the same deterimental effect
upon flexural properties as too low a level. Based upon these
data, we fabricated all subsequent samples with the optimum
level of 55% of carbon fiber reinforcement.

In the earlier carbon fabric laminates, we used very little
pressure to fuse the layers of polymer and relied almost entirely
upon heat to effect the lamination. To improve the lamination by
removing any voids or imperfections, we made laminates under
various pressures. However, we found that the higher pressures
caused the PLA material to spread out from the laminate with the
result that very little polymer was left to bond together the car-
bon layers. To counteract this effect, we fabricated a mold
which was open only at the top. The PLA and carbon films were

TABLE I. FLEXURAL PROPERTIES OF CARBON FABRIC LAMINATES WITH POLY(DL-LACTIDE)

Carbon,%	Pressure on Mold	Type of Mold	Flexural Strength, $\times 10^3$ psi	Flexural Modulus, $\times 10^6$ psi
43	High	Open	14.6	0.56
55	High	Open	18.0	0.92
57	High	Open	13.7	1.09
67	High	Open	8.4	0.49
57	Low	Open	20.6	0.78
57	Low	Closed	18.6	0.79
55	High	Closed	26.2	1.20

placed in the mold in alternate layers, and pressure was then applied from the top. This procedure gave better results since only a small amount of polymer flashing was observed around the top of the mold.

The data in Table I show the effect of pressure on the mold during the lamination process. The open mold with a low pressure gives laminates with better flexural strength than those produced in open molds with high pressures. Apparently, the higher pressure on the open molds forces the PLA material out of the laminate and yields a composite with a higher level of carbon than desired.

As expected, the properties of the laminates produced with low mold pressure are not affected by the type of mold used in the lamination. However, the properties of the laminates produced with high pressure are significantly influenced by the type of mold as shown by the two samples in the table with 55% of carbon. The values of flexural strength and flexural modulus determined with the laminate containing 55% carbon made in the closed mold with high pressure were the best obtained in this series of laminates.

However, the fabrication of closed molds with various dimensions and the release of the composite from these molds presented difficulties. Therefore, we modified the procedure for the use of open molds, and we were able to obtain high-strength composites without the earlier problems of sample spreading and excessive flashing.

In the improved procedure, alternate layers of PLA and fibrous-reinforced PLA are fused one layer at a time in a press at 70-75°C and 2,000-3,000 psi. Generally, the fibrous film which is located on the exterior of the composite is fused to a film of PLA, and the resulting composite is fused to another layer of fibrous film. In the initial samples, we prepared composites with 5 layers of fibrous film and 4 layers of PLA film. At the temperatures and pressures employed in the improved procedure, we encountered only minor amounts of composite flashing or spreading.

The fibrous-reinforced laminates with PLA were tested for flexural strength according to ASTM D 790. From the stress-strain curves, we calculated the tangent modulus of elasticity according to standard ASTM methods. The results of these tests with several of the fibrous-reinforced composites are given in Table II, along with the polymer inherent viscosity, the sample thickness, and the force required to bend the sample to its breaking point.

The data in Table II support several important hypotheses and concludions that we presented earlier in the program. First, the continuous-filament yarns yield composites with higher flexural properties than those with fabric reinforcement. This result is expected since in the fiber-reinforced materials, all the fibers are parallel and contribute to the flexural strength. In the

Table II. FLEXURAL PROPERTIES OF FIBROUS-REINFORCED LAMINATES WITH POLY(DL-LACTIDE)

Fiber	Polymer Viscosity, dL/g	$\overline{L}^a$, lb	$\overline{S}^b$, x10^3 psi	$\overline{E}^c$, x10^8 psi	Sample Thickness, in.
Nextel 312 Ceramic yarn	1.14	119.6	28.4	1.8	0.159
Nextel 312 Ceramic fabric	1.14	24.1	11.6	1.3	0.116
Thornel 300 Carbon yarn	1.14	48.8	24.3	1.7	0.109
Rayon VCL Carbon fabric	1.27	27.5	12.7	0.6	0.115
Rayon VCL Carbon fabric	0.58	33.8	20.9	0.8	0.102

a. Average breaking load

b. Average flexural strength

c. Average flexural modulus

fabric-reinforced materials, half of the fibers are in a direction in which they do not contribute to flexural properties, and the composites are weaker. The flexural properties of the fiber-reinforced composites are superior to that of bone and equivalent to the target values established in our research proposal. These materials are not completely biodegradable, however, and serve only as a model for designing systems with sufficient strength and rigidity.

A second conclusion confirmed by the data in Table II is that within the range studied, higher-molecular-weight PLA does not yield composites with improved initial flexural properties. In fact, the lower-molecular-weight PLA (0.58 dL/g inherent viscosity) gave a composite with carbon fabric which displayed better flexural strength than a similar composite with PLA of higher molecular weight (1.14 dL/g inherent viscosity). This same result was seen in our earlier tests with non-reinforced PLA samples. Apparently, the long chains of the high-molecular-weight polymer provide more flexibility due to entanglement with adjacent chains, whereas the shorter chains afford greater rigidity.

A third fact emphasized in Table II is that the values of flexural strength and flexural modulus are independent of the sample thickness since that value has been used in the calculations to derive the flexural properties. However, the load or force required to break the sample is a function of sample size. Thus, although the ceramic and carbon yarn composites have almost identical flexural properties, the ceramic yarn composite with a thickness of 0.159 in. will resist at least twice the force before breaking of the carbon yarn composite with a thickness of only 0.109 in.

C. Property Retention: In Vitro Test Results

Although the fibrous-reinforced laminates possessed satis-factory initial flexural properties, the retention of these properties in vivo for several weeks is essential to their successful use as mandibular cribs. To simulate in vivo conditions, we exposed the fibrous-reinforced laminates to a phosphate-buffered saline solution (0.2 $\underline{M}$, pH 7.4) at 37°C for 2, 4, 6, and 8 weeks. After the appropriate exposure time, the samples were removed, blotted dry, and conditioned for 24 hours in a room with controlled temperature and humidity. The conditioned samples were then tested for flexural proper-ties.

The results of our in vitro degradation studies are shown in Tables III- V. The flexural strength and flexural

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TABLE III. RETENTION OF FLEXURAL PROPERTIES FOR
CARBON FABRIC-REINFORCED LAMINATES

Exposure[a] Time, days	$\bar{L}$,[b] lb	$\bar{S}$,[b] $\times 10^3$ psi	$\bar{E}$,[b] $\times 10^6$ psi	Sample Thickness, in.
0	75.4	15.0	0.8	0.182
14	46.2	9.8	0.5	0.172
28	51.2	8.8	0.5	0.193
42	43.9	7.0	0.4	0.207
56	33.7	3.9	0.3	0.214

a. Phosphate-buffered saline solution at 37°C.

b. See Table II for explanation.

TABLE IV.   RETENTION OF FLEXURAL PROPERTIES FOR
CERAMIC YARN-REINFORCED LAMINATES

Exposure[a] Time, days	$\bar{L}$,[b] lb	$\bar{S}$,[b] $x10^3$ psi	$\bar{E}$,[b] $x10^6$ psi	Sample Thickness, in.
0	129.3	39.6	2.5	0.143
14	71.5	19.4	1.5	0.153
28	50.2	12.2	0.8	0.172
42	52.6	11.3	1.1	0.175
56	54.0	10.9	1.2	0.180

a. See Table III for explanation.

b. See Table II for explanation.

TABLE V.   RETENTION OF FLEXURAL PROPERTIES FOR
THINNER CERAMIC YARN-REINFORCED LAMINATES

Exposure[a] Time, days	$\bar{L}$,[b] lb	$\bar{S}$,[b] $x10^3$ psi	$\bar{E}$,[b] $x\ 10^6$ psi	Sample Thickness, in.
0	27.1	31.3	2.5	0.078
14	33.7	26.5	2.4	0.094
28	29.4	24.9	2.3	0.095
42	27.3	23.8	2.2	0.090
56	28.0	23.7	2.0	0.092

a. See Table III for explanation.

b. See Table II for explanation.

modulus values are also presented graphically in Figures 1 and 2. As expected, the data from our tests show a decrease in flexural properties of the samples with their exposure to the saline solution. However, we were surprised at the rapid rate of decrease in properties with the samples prepared with carbon fabric and ceramic yarns. The carbon fabric-reinforced samples had only marginal flexural strength and flexural modulus values initially, and within two weeks the flexural properties of these samples degraded to unacceptable values. The ceramic yarn-reinforced samples had superior values of flexural properties initially, but within four weeks, these values had decreased to marginal levels.

Interestingly, the thinner samples of ceramic yarn-reinforced PLA identical to those sent to the Army for in vivo tests show a much better retention of properties. Even after eight weeks, the thinner samples yielded excellent values of flexural strength and flexural modulus. We suspect that the better retention of properties was probably due to improvements in lamination with the thinner samples.

As mentioned earlier, the flexural properties are in-dependent of the sample thickness, but the load required to break the samples is proportional to the thickness of the plate. Thus, the thicker samples of ceramic yarn-reinforced materials even after 8 weeks of exposure require almost twice the force to break as the thinner samples. These values shown in Tables IV and V are also important for successful mandibular stabili-zation.

D. Reinforcement with Carbon and Ceramic Yarns

As a result of the test data presented in the previous sections, we focused our subsequent reinforcement efforts on the use of carbon and ceramic yarns. We prepared new fiber-reinforced composites from PLA with inherent viscosity values of 0.67 and 1.04 dL/g as measured in chloroform at 30°C. These viscosity values represent low- and medium-molecular-weight polymers respectively.

The fiber-reinforced composites were prepared by the same general procedure as described previously. Films of PLA with the appropriate viscosity values were fabricated and then laminated with fiber-reinforced films of the same polymer. The reinforcing fibers consisted of both carbon and ceramic materials. The carbon fibers were Thornel 50 yarns produced by Union Carbide from carbonization of polyacrylonitrile (PAN). The ceramic fibers were Nextel AB 312 obtained from 3M Company and Fiber FP developed by DuPont.
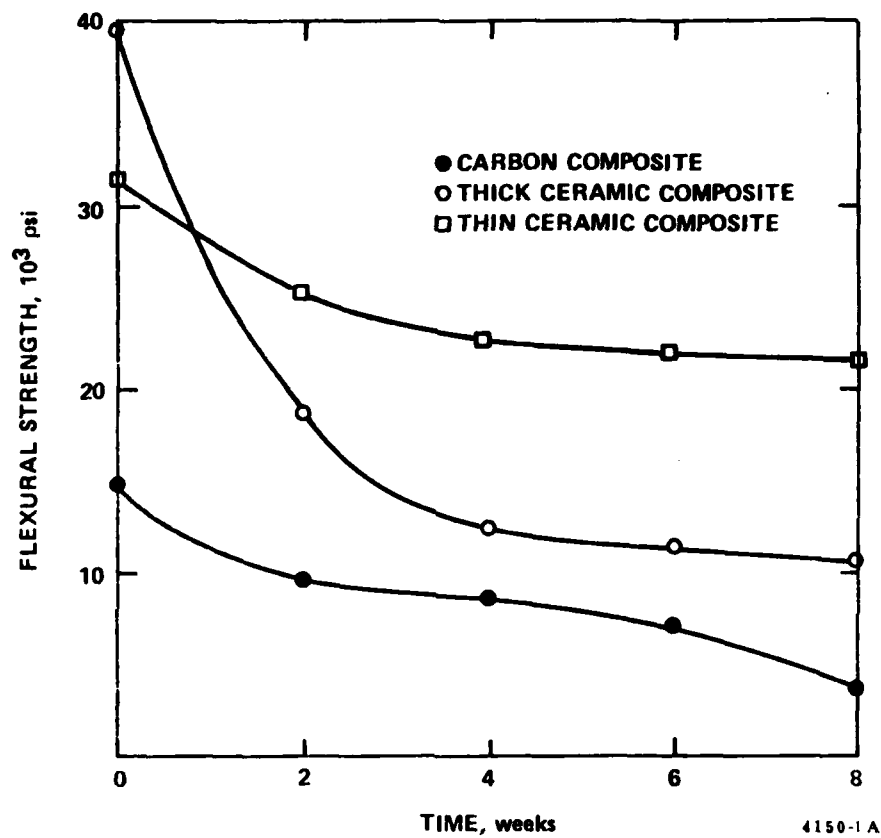
Figure 1.   Effect of in vitro exposure on
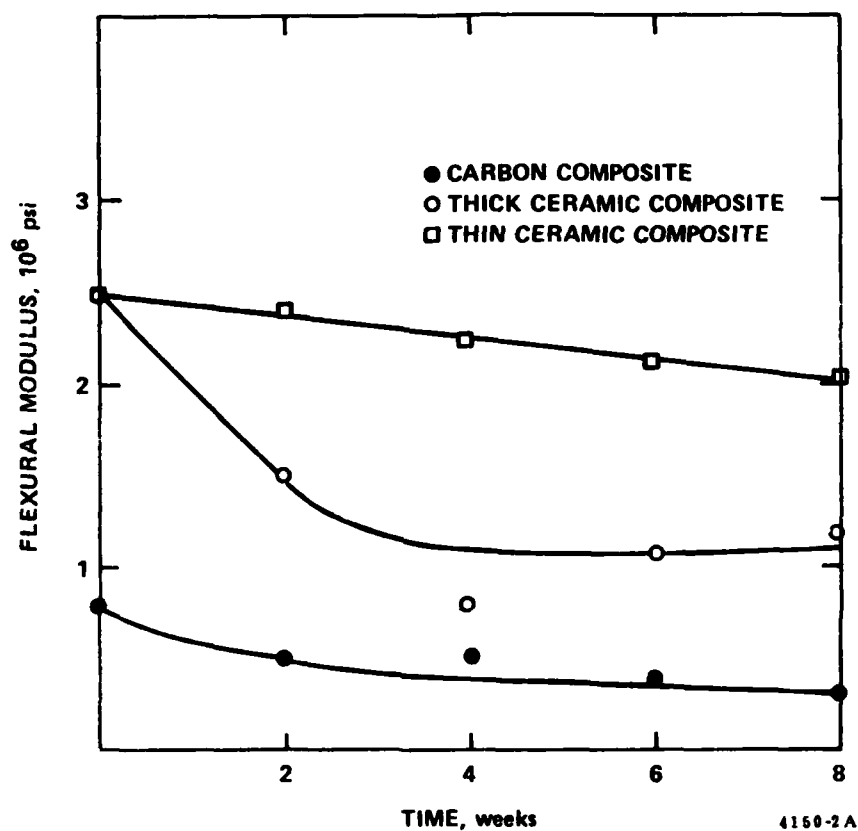flexural strength values.

Figure 2. Effect of in vitro exposure on flexural modulus values.

As reported previously, we were able to obtain high-strength composites using our open-mold lamination procedure. In this process, alternate layers of PLA and fiber-reinforced PLA are fused one layer at a time in a press at 70-75°C and 2,000-3,000 psi. Since initial animal experiments conducted by the Army suggested that we needed thinner composite plates, we prepared the new composites with four layers of fiber-reinforced film and three layers of PLA film.

E. Determination of Flexural Properties of Yarn-Reinforced Materials.

The fiber-reinforced laminates with PLA were tested for flexural strength and modulus according to ASTM D 790. The results of these tests are given in Table VI with data also on the inherent viscosity of the polymer, the sample thickness, and the force required to bend the sample to its breaking point.

The data in Table VI show that we have achieved our proposed target values for PLA bone plates of 20,000 psi for flexural strength and 2×10^6 psi for flexural modulus. In fact, the values obtained with the low-molecular-weight PLA and Thornel 50 carbon fiber composite are much higher than we had anticipated. Based upon these results, this particular composite can be prepared in very thin plates and still provide satisfactory structural integrity for bone fixation.

As we had expected from our earlier work, the low-molecular-weight PLA gave composites with higher values of flexural properties. However, the major factor in composite strength appears to be the type of reinforcing fiber. The Thornel 50 carbon fiber gave laminates with the highest values of flexural properties followed by Nextel AB 312 ceramic fibers and then by Fiber FP. A possible explanation for these results may be derived from the tensile properties of the various fibers as shown in Table VII. The tensile strength of the Thornel 50 yarn is greater than that for the two ceramic fibers. In fact, the flexural properties of the composites tend to compare in relative order with the tensile strengths of the fibrous rein-forcement. Tensile modulus values of the reinforcing fibers do not appear to be as important for composite properties as do the tensile strength values. This fact is illustrated by both Thornel 50 and Fiber FP having essentially the same tensile modulus values, but the flexural properties of composites from these two materials are quite different.

Although the flexural properties of the PLA composites tend to correlate with the tensile-strength values of the reinforcing fibers, another factor may be responsible for some of the observed differences. Some of the high-modulus rein-forcing fibers are coated with an organic polymer as a size

TABLE VI. FLEXURAL PROPERTIES OF FIBER-REINFORCED LAMINATES
FROM LOW- AND MEDIUM-VISCOSITY POLY(DL-LACTIDE)

Fiber	Polymer Viscosity, dL/g	$\bar{L}^a$, lb	$\bar{S}^a$, $\times 10^3$ psi	$\bar{E}^a$, $\times 10^6$ psi	Sample Thickness, in.
Nextel AB 312	1.04	77.7	23.5	1.3	0.161
Nextel AB 312	0.67	27.2	27.5	2.0	0.083
Thornel 50	1.04	144.7	25.3	1.6	0.215
Thornel 50	0.67	61.1	47.9	5.7	0.091
DuPont Fiber FP	1.04	58.3	10.1	1.1	0.215
DuPont Fiber FP	0.67	62.5	14.1	1.5	0.170

a. See Table II for explanation.

Table VII. MECHANICAL PROPERTIES OF REINFORCING FIBERS

Fiber	Tensile Strength, $x10^3$ psi	Tensile Modulus, $x10^6$ psi
Thornel 50	320	57
Nextel AB 312	250	22
Fiber FP	200	55

to improve the compatibility and wettability of the fibers to impregnating resins. Thus, the Thornel 50 yarns contain an acrylic size, the Nextel AB 312 fibers normally contain either an acrylic or polytetrafluoroethylene size, and the Fiber FP yarn contains a small amount of silica size. The size on the reinforcing fiber probably influences the adhesion of the polymer to the fiber with resultant changes in flexural properties.

The fiber-reinforced PLA composites prepared with low- and medium-viscosity polymer were also subjected to in vitro degradation tests. Degradation studies on control samples with no fiber reinforcement were also conducted. For the degradation studies, we employed a phosphate-buffered saline solution (0.2 $\underline{M}$, pH 7.4) at 37°C. Samples were removed after 2, 4, 6, and 8 weeks and tested for retention of inherent viscosity and flexual properties. All samples were dried at 70°C overnight and conditioned in a constant-temperature and constant-humidity room before being broken in the standard flexual test. For viscosity measurements, we dissolved the samples in dichloromethane, filtered the solution to remove the reinforcing fibers, and evaporated the dichloromethane under conditions of heat and vacuum. This procedure not only served to remove fibers, but it also ensured a more homogeneous sample for viscosity measurements. The inherent viscosity of the polymer was then measured in chloroform at 30°C.

The results of the degradation studies for low- and high-molecular-weight samples are presented in Figures 3-8. These figures show the same decrease in flexual properties with exposure time as observed for other composites. The loss in flexual properties of the composite is assumed to result from hydrolytic degradation of the polymer, which leads to delamination of the films or voids in the composite. These voids create cracks and weak spots in the laminate with a subsequent loss in strength.

The viscosity losses shown in the figures follow the expected behavior. We obtained an almost linear decrease in viscosity during the first several weeks, but the rate of decrease slowed, for initially high-molecular-weight material, during the last weeks as lower-molecular-weight polymer was formed. Hydrolysis of the long molecular chains of higher-molecular-weight polymer leads to short chains with a rapid decrease in viscosity. This effect becomes less pronounced with hydrolysis of the shorter polymer chains.

Although the rate of decrease in polymer viscosity was similar to that predicted, the values of the polymer viscosity were lower than what we had expected. In fact, the polymer recovered from the fiber-reinforced composite with no exposure to in vitro conditions was considerably lower in viscosity

Figure 3. Effect of in vitro exposure on flexural strength of fiber-reinforced low viscosity PLA laminates.

Figure 4. Effect of in vitro exposure on flexural modulus of
fiber-reinforced low viscosity PLA laminates.
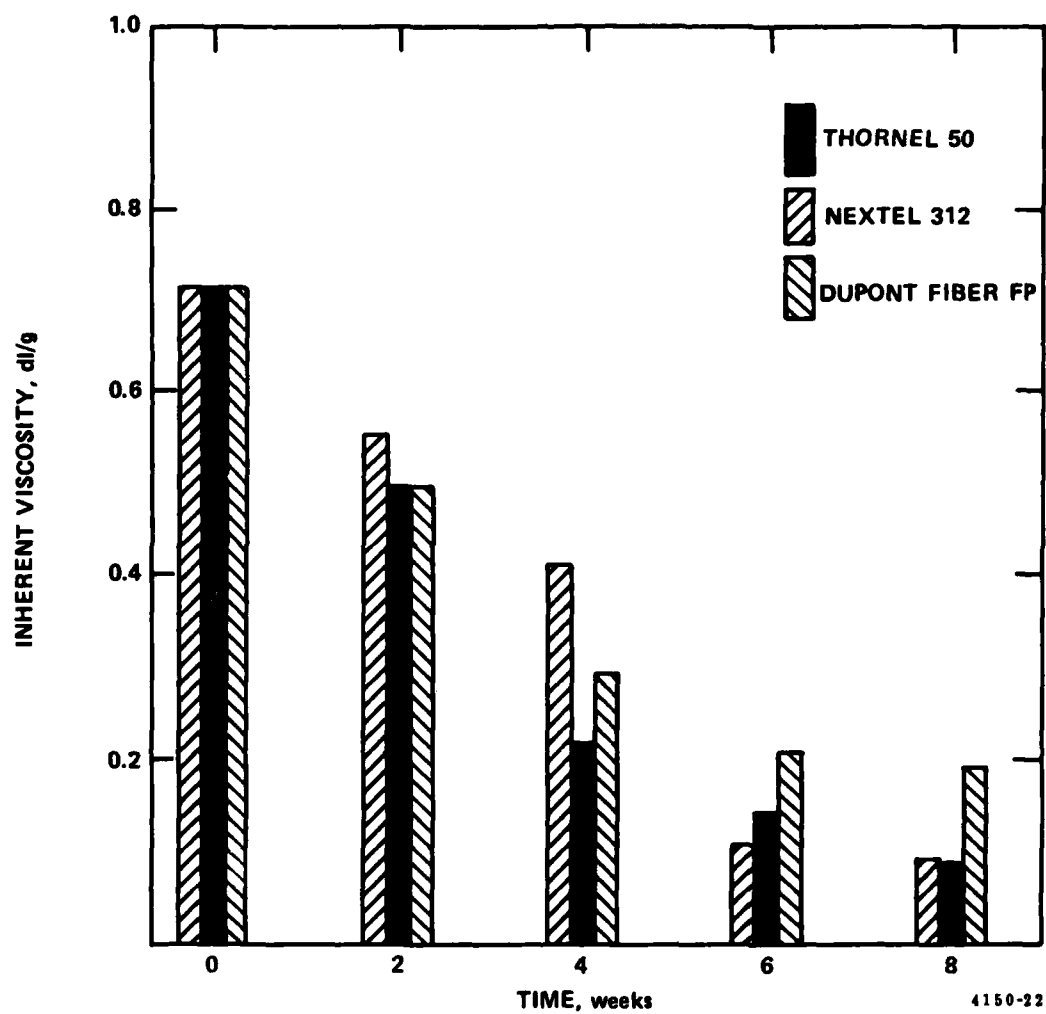
Figure 5. Effect of in vitro exposure on inherent viscosity of
low-molecular-weight PLA laminates.

Figure 6.   Effect of in vitro exposure on flexural strength of
fiber-reinforced high-viscosity PLA laminates.

FLEXURAL MODULUS, 10^6 psi

- **THORNEL 50**
- **NEXTEL 312**
- **DUPONT FIBER FP**

1.6

1.2

0.8

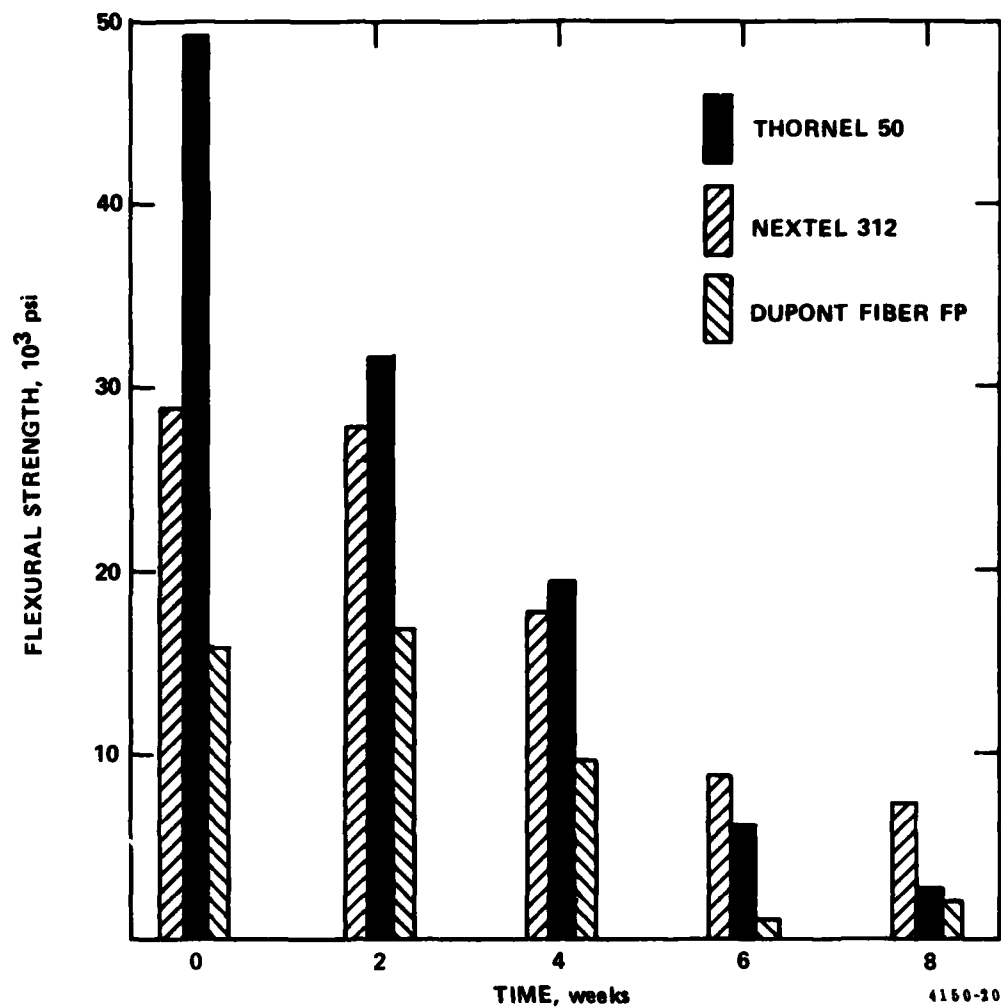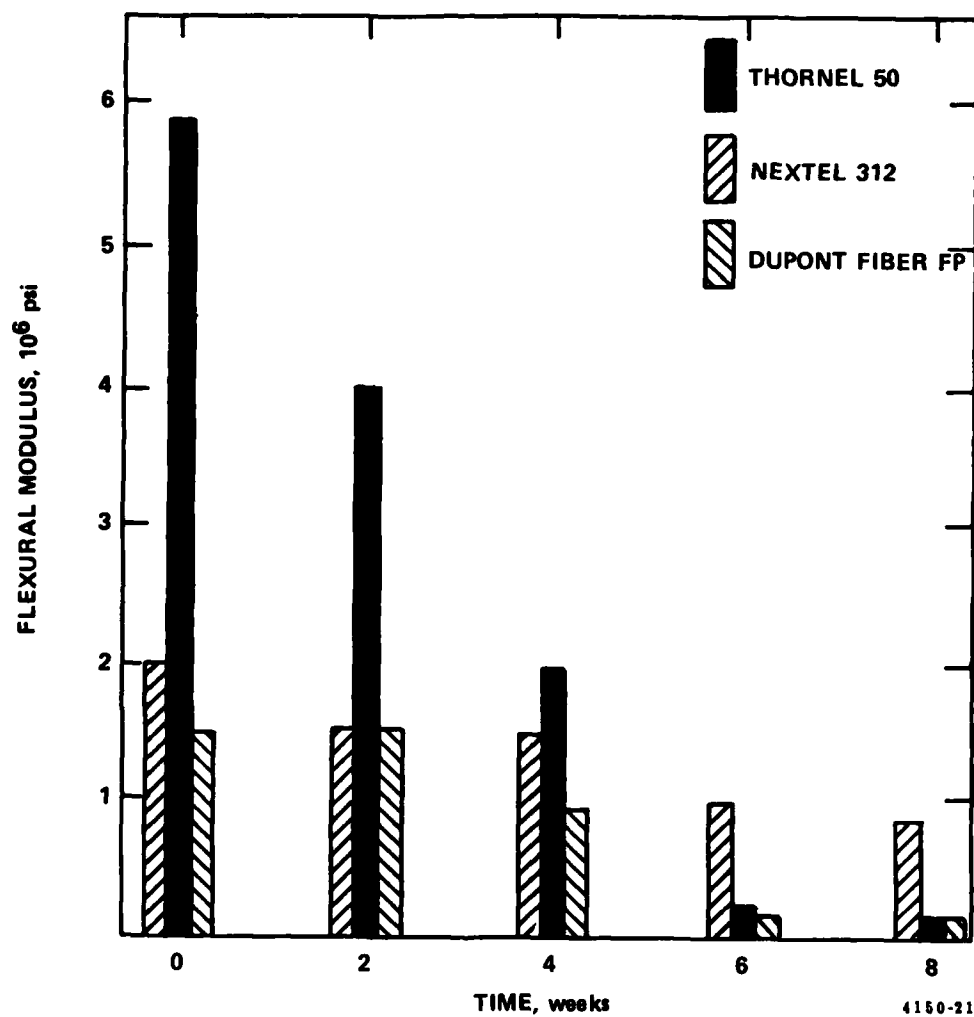0.4

0   2   4   6   8

TIME, weeks

4150-15

Figure 7.   Effect of in vitro exposure on flexural modulus of
fiber-reinforced high-viscosity PLA laminates.

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Figure 8. Effect of in vitro exposure on inherent viscosity of fiber-reinforced high-viscosity PLA laminates.
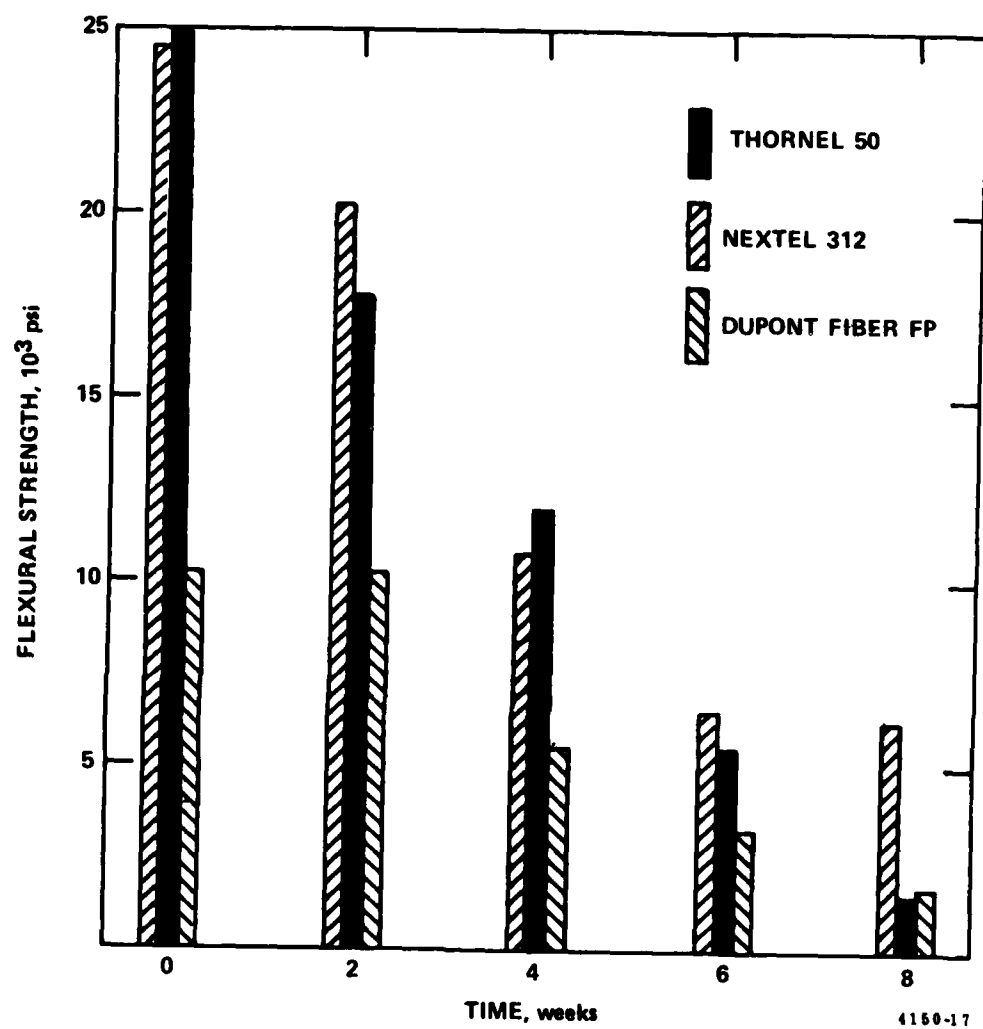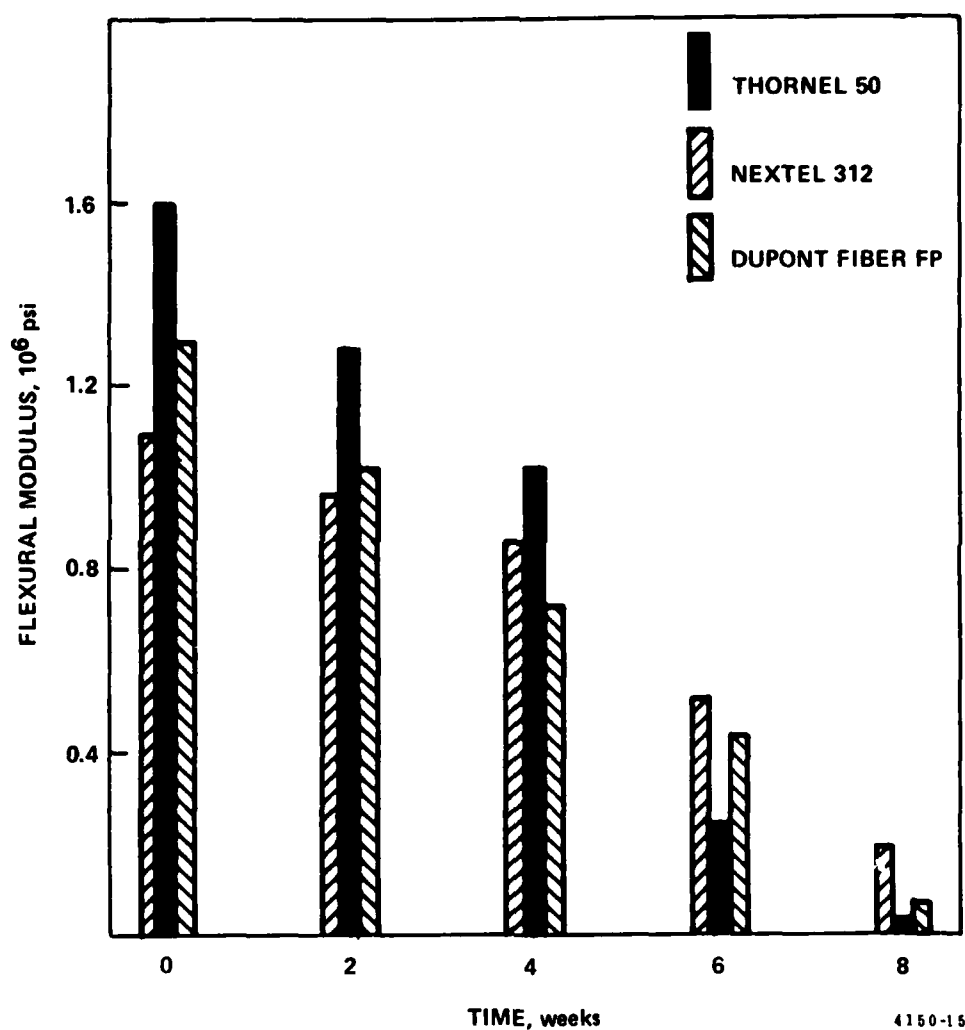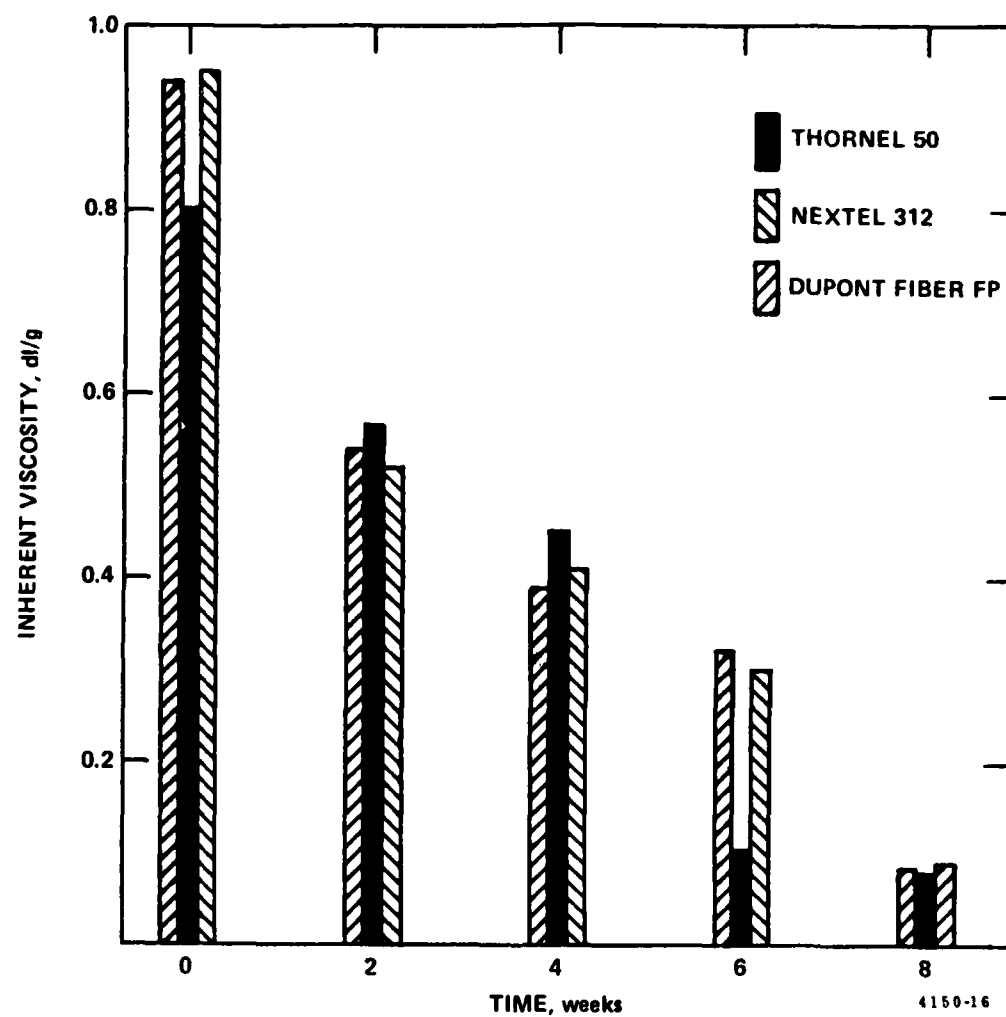
(0.82 dL/g) than that of the original polymer (1.27 dL/g). Since we had made nonfibrous-reinforced PLA laminates in earlier experiments with essentially no loss in polymer viscosity, we suspected the procedure for recovery of the polymer from the fiber reinforcement to be responsible for the sudden decrease in viscosity. However, a nonfibrous-reinforced PLA laminate when subjected to the same recovery procedure gave essentially no loss in viscosity. Therefore, we concluded that the fibrous reinforcement was the cause of the drop in viscosity. Because these fibers contain small amounts of size for processability purposes, we suspect the size blended with the PLA during the recovery operation, with a resultant change in viscosity. The ratio of size to polymer would remain fairly constant in the samples, and the effect on polymer viscosity should be similar in all the samples.

During the in vitro degradation studies, we also determined the weight loss of the exposed samples after two, four, six, and eight weeks. The samples were removed from the phosphate-buffered saline solution, dried overnight at 70°C, and conditioned in a constant temperature and humidity room before being weighed. We found such small weight losses during the eight weeks of study that precise weight-retention percentages were difficult to determine. These results agree with those of other investigators who found very little weight loss with PLA until the polymer had degraded to a material with such low molecular weight as to be water soluble.

Even though the three fibers used for reinforcement in these samples are not biodegradable, the degradation study shows the gradual loss of flexural strength and modulus of elasticity, which may be expected in any fiber-reinforced system with PLA. This degradation, producing a gradual loss of laminate strength, permits an increasing transfer of load to the developing bone. The gradual load transfer to the newly forming bone results in considerably stronger bone scaffolding by reducing "stress-protection" atrophy.

Our in vitro data indicate that satisfactory flexural properties are maintained for four to six weeks. After this period, new bone should have formed, and it should be able to support part of any external load. Preliminary evidence from the in vivo study in canines conducted by the Army with these fiber-reinforced biodegradable plates showed good bone growth and stability.

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V. SELECTION OF STERILIZATION PROCEDURE

The PLA composites must be sterilized before use as mandibular cribs. Sterilization by gamma irradiation or ethylene oxide appear to be the only methods available since steam autoclaving causes a significant degradation of the polymer. We typically use gamma irradiation for the sterilization of PLA microcapsules produced in our laboratories. The effect of irradiation on the load-bearing character of PLA polymer, however, had not been determined. We used both ethylene oxide and gamma irradiation to sterilize composites containing PLA with viscosities of 0.67 and 1.04 dL/g to determine which procedure was the more acceptable.

The gamma-irradiation sterilization consisted of an exposure of the composite plates to 2.0 megarads of irradiation from a cobalt-60 source. Ethylene oxide sterilization was achieved by exposure of the samples to ethylene oxide for three hours at 60°C. The sterilized samples were then tested for retention of flexural properties and inherent viscosity. The results of these tests are summarized in Tables VIII and IX.

The data in Tables VIII and IX show a greater loss in polymer viscosity with gamma-irradiation than with ethylene oxide sterilization. Gamma irradiation caused about a 25% loss in viscosity of all polymer samples. Apparently the irradiation causes chain clevage of the polymer. With ethylene oxide exposure, we observed essentially no loss in polymer viscosity. However, both sterilization methods decreased the flexural properties of the composites. The retention of the original flexural properties appears to be dependent upon the polymer viscosity, the type of reinforcing fiber, and the method of sterilization. The higher-viscosity polymer seems to yield somewhat better retention of flexural properties. The composites with ceramic fibers also have a better retention of properties than those with the carbon yarns. The DuPont Fiber FP gives the best retention of flexural properties for any of the composites; however, it should be noted that the initial values of flexural strength and modulus are quite low for this fiber-reinforced material. Based upon the results of these tests, we recommend ethylene oxide as the preferred method for composite sterilization.

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TABLE VIII. EFFECT OF STERILIZATION ON HIGH-VISCOSITY POLYLACTIDE COMPOSITES

	Retention of Properties after Sterilization, %					
	Gamma Irradiation			Ethylene Oxide		
Composite	$\bar{S}^a$	$\bar{E}^a$	IV^b	$\bar{S}$	$\bar{E}$	IV
Nextel 312	68	54	71	105	100	100
Du pont Fiber FP	86	100	70	95	100	94
Thornel 50	92	75	73	80	56	101

a. See Table II for explanation.

b. Inherent viscosity.

TABLE IX. EFFECT OF STERILIZATION ON LOW-VISCOSITY POLYLACTIDE COMPOSITES

	Retention of Properties after Sterilization, %					
	Gamma Irradiation			Ethylene Oxide		
Composite	$\bar{S}^a$	$\bar{E}^a$	IV^b	$\bar{S}$	$\bar{E}$	IV
Nextel 312	64	50	75	58	45	95
Du pont Fiber FP	100	107	86	83	80	109
Thornel 50	62	32	81	84	57	102

a. See Table II for explanation.

b. Inherent viscosity.

VI.   PREPARATION OF PLATES FOR THE ARMY'S CANINE MANDIBULAR REPAIR STUDY

We prepared samples of fiber-reinforced laminates for evaluation by the Army in a canine implant study concerned with the repair of mandibular fractures. The Army reported that in earlier mandibular repair experiments with polylactic acid materials, the polymeric bone plates warped to such extents that they actually pulled the bone screws from the mandible. We developed methods for preventing the warpage, and we examined harvested plates for retention of initial properties and material integrity.

A.   Prevention of Warpage

For our initial samples of mandibular cribs, we prepared large sections (3 x 4 in.) of the thicker samples of ceramic yarn-reinforced PLA, heated them to approximately 50°C, and bent them around a rod to obtain the desired curvature. We then immersed these samples in the phosphate-buffered saline solution at 37°C for various times and measured the distance between the ends of the plates. The cribs almost completely opened up after only 2-4 days of exposure. Apparently, stresses were placed in the crib during the bending operation, and upon exposure to heat, the sample tended to return to its original configuration to relieve the built-in stresses.

To avoid any warpage of the cribs, we annealed several samples to remove the built-in stresses generated during the bending operation. The process of annealing, commonly used with polymers and glass, consists of heating the material in its bent shape for extended periods to allow the stress points to dissipate. We heated our ceramic yarn-reinforced samples at 70°C for several hours. The temperature we chose was above the glass-transition temperature of the polymer so that the polymer chains would have sufficient mobility to relieve any stresses.

The results of our annealing experiments, as shown in Table X, indicate a significant decrease in warpage. The control samples opened up completely in four days, but the annealed samples maintained fairly good conformation. Two samples which were bent into cribs and annealed for 16 hours were sent to the Army for in vivo testing in dogs.

We also used another method to prevent warpage of the sample cribs. The Army indicated that the center or bent portion of the tray did not have to be thick or strong since it was only used to hold bone chips in place for remodeling of the mandible. Consequently, we prepared two bone plates with 4 layers of ceramic yarn-reinforced PLA and 3 layers of PLA. We then spaced the two plates about one-inch apart and

TABLE X.   EFFECT OF ANNEALING ON STABILITY
OF MANDIBULAR CRIBS

Exposure[a] Time, days	Separation Between Plates, in.		
	Control	Annealed 4 h	Annealed 7 h
1	0.615	0.745	0.545
2	0.826	0.843	0.580
4	open	0.855	–
5	–	0.857	–
6	–	–	0.695
7	–	0.857	0.695
11	–	0.880	–
21	–	0.940	0.890

a.   See Table III for explanation.

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bridged them together by laminating a fourth layer of PLA over both plates. This process gave two reinforced plates connected with a flexible hinge of PLA polymer. Since the film of PLA used as the hinge or bent portion of the crib is quite thin, it does not have sufficient strength to warp the two reinforced plates even if slight stresses are generated during the bending operation. Six mandibular cribs fabricated in this fashion were sent to the Army for in vivo testing.

B. Evaluation of Plates Harvested from Canine Implant Study

During the third year of the contract, we received three dog mandibles from USAIDR. These mandibles had been fractured and repaired with bone plates that we supplied to the Army in 1980. The plates comprised PLA reinforced with Nextel 312, a nonbiodegradable ceramic fiber from 3M Corporation. The mandibles represented in vivo test periods of 3, 8, and 12 weeks. The polymeric bone plates were removed from the dog mandibles, and standard flexural test and molecular-weight determinations were performed.

Prior to their flexural testing, we dried the samples in an oven at 90°C overnight and conditioned them for 24 hours in a constant-temperature and-humidity room. Following the flexural testing, we dissolved the bone plates in dichloromethane. The ceramic fibers were removed by filtration, and the dichloromethane was then removed with vacuum and heat at 60°C overnight. We next dissolved small quantities of the recovered polymers in chloroform for viscosity determinations. Results are shown in Table XI.

The in vivo data correlate with our in vitro tests in that there is a loss with time of both flexural strength and flexural modulus. There is also a corresponding decrease in viscosity. The viscosity values from the in vivo samples are somewhat higher than those we obtained in the in vitro evaluations, but these higher values are understandable if we consider the difference between the two test conditions. In vitro tests were done by complete immersion of the laminate in a phosphate-buffered saline solution (0.2 $\underline{M}$, pH 7.4) at 37°C. With the in vivo studies, the plates do not experience total immersion, and there is additional protection from hydrolysis by the growing over-burden of tissue and bone.

Although the flexural properties of the in vivo plates show the same trend with time as those of the in vitro samples, the values are significantly different. The values of the flexural properties for the in vivo plates are lower by a factor of at least 10 than those of the in vitro samples. Since the polymer viscosities and molecular weights of both samples are approximately the same, we conclude that the lower flexural properties of the in vivo samples are not due to differences in the polymers. One cause for the lower flexural values could be the presence of biological fluids or body tissue components in the in vivo samples which function as plasticizers to decrease

TABLE XI. PROPERTIES OF REINFORCED POLY(DL-LACTIDE)
BONE PLATES AFTER IN VIVO EXPOSURE

Exposure[a] Time, weeks	$\bar{S}^a$, psi	$\bar{E}^b$, psi	IV^c, dL/g in $CHCl_3$
3	1075	26,000	0.59
8	300	6,060	0.42
12	50	940	0.36

a. Flexural strength

b. Flexural modulus

c. See table VIII for explanation.

the flexural properties. To examine this factor, we plan to expose similar laminated plates to serum for various times and compare their properties to those obtained with the buffered-saline solution.

Another more likely cause for the lower flexural values could be the influence of sterilization upon in vivo degradation. Our in vitro degradation studies were conducted on nonsterilized samples. The plates recovered from the dogs had been sterilized by gamma irradiation before implantation. In Section V we show-ed that sterilization by gamma irradiation caused a loss in flexural properties of approximately 40% for DL-PLA laminates reinforced with Nextel 312 ceramic fibers. These losses in flexural properties were obtained on samples which had not been exposed to in vitro conditions. With this precipitous loss in properties of virgin samples with gamma irradiation, both in vitro and in vivo degradation rates for flexural properties could be accelerated to give the low values that we obtained from the animal studies.

Therefore, we have prepared additional samples of PLA reinforced with Nextel 312 ceramic fibers for further study. We are currently examining the in vitro degradation rate of both sterilized and non-sterilized fiber-reinforced plates.

Regardless of which mechanism is responsible for the loss in flexural properties, the values we obtained on the plates recovered from test dogs illustrate several important factors. The mandibles healed well with the polymer plates even though the plates were relatively weak after three weeks of implantation as fixation devices. Perhaps the flexural properties required for long-term stabilization are less than those we had estimated. The rapid loss of flexural strength for sterilized polymer samples with in vivo implantation time indicates that bone plates with high initial values of flexural properties are required for satisfactory stabilization of the mandible during the first several weeks of repair. This factor could explain the failures observed by the Army in earlier studies with nonreinforced polymer plates.

VII. TOTALLY BIODEGRADABLE FIXATION SYSTEMS

The results with the carbon and ceramic fiber-reinforced composites demonstrate that PLA plates can be fabricated with flexural properties equivalent to or greater than those of bone. Additionally, the preliminary in vivo studies by the Army with these plates in dogs indicate acceptable stability and performance. However, the carbon and ceramic fibers are not biodegradable. In order to develop a totally biodegradable fixation plate with acceptable initial properties and property retention, we investigated a number of design and fabrication modifications. We examined replacement of ceramic and carbon reinforcing fibers with biodegradable fibers, injection molding of PLA, orientation of laminates, reinforcement with biodegradable ceramics, and cross-linking of two biodegradable polymers--PLA and copolyoxalate.

A. Reinforcement with Biodegradable Fibers

We first examined commercially available biodegradable fibers for use in reinforcing PLA plates. Polyglycolic acid (PGA) sutures (Davis and Geck Laboratories) were drawn to their maximum length by application of 2000-g load for 15 minutes at 60°C. These high-modulus, low-elongation fibers were then laminated with PLA. The temperature was maintained below 40°C during the lamination process to prevent the possible relaxation of the drawn fibers. Subsequently, the laminates were sectioned to provide specimens for standard flexural tests. The results are shown in Table XII.

The flexural strength of the laminates decreased, but the flexural modulus increased slightly. The flexural modulus, however, was still insufficient for use of the PGA-reinforced plates in fracture fixation. As a result, we abandoned the use of PGA suture material and turned our attention to the development of high-modulus, low-extensibility, biodegradable reinforcing fibers.

Our first attempt at obtaining high-modulus biodegradable fibers was the precipitation of the polymer from a vigorously stirred solution by addition of a nonsolvent. The shearing action created by the stirring causes fibrils to form. These fibrils are highly crystalline and oriented. Because of its solubility in many common solvents and its crystalline nature, we used polycaprolactone, a biodegradable polymer, to generate our first fibrils. A polycaprolactone solution in methylene chloride was slowly added to a rapidly stirred methanol bath. The fibrils that formed were collected on a paper machine to yield a sheet of nonwoven material. A section of the nonwoven polycaprolactone sheet was laminated between two thin films of PLA at 70°C and 1,000-2,000 psi. The sheet of polycaprolactone fused to the PLA films yielding a clear laminate with no enhancement of flexural properties. Apparently, the lamination operation destroyed the crystallinity and orientation of the polycaprolactone fibrils. We attributed this effect to the low glass-transition temperature and melting point of polycaprolactone.

TABLE XII. EFFECT OF PGA FIBER REINFORCEMENT
ON LAMINATE FLEXURAL PROPERTIES

PGA FIBER REINFORCEMENT		$\overline{S}$,[a] $\times 10^3$ psi	$\overline{E}$,[a] $\times 10^3$ psi
Level, %	Orientation		
--	-	7.28	0.33
50	Undrawn	2.30	0.09
15	Drawn	5.60	0.37

a. See Table II for explanations.

A similar precipitation experiment with poly(L-lactide) (L-PLA) from the same solvents did not yield fibrils, but rather an agglomerated mass of polymer.

Polyglycolic acid (PGA) is a highly crystalline and high-melting biodegradable polymer. However, it is only soluble in a few selected solvents. We dissolved PGA in hexafluoroacetone sesquihydrate and added it slowly to a rapidly stirred methanol bath. A slightly fibrous material precipitated, but upon filtration and drying, it became a powder. The addition of the PGA-hexafluoroacetone solution to methanol without stirring gave a continuous filament of yarn which was fragile and weak.

Our second method of producing high-modulus biodegradable fibers was to grow them in solution using sonic frequencies. This procedure is based upon work published by scientists at Hughes Aircraft Company in generating three-dimensional (3-D) polypropylene fibers in situ. Researchers at Hughes found that sonic agitation of polymer solutions under the proper conditions could produce fibers. The resulting fibers, which are formed in a 3-D array, have outstanding tensile strength. Because the fibers are grown in situ, reinforcement occurs not only in all directions, but also in voids and crevices that would be potentially weak spots in the sample. Biodegradable fibers produced by this technique could provide the high-strength, high-modulus material needed for reinforcement of biodegradable polymers.

We first attempted to reproduce the results obtained by the Hughes scientists. They used a solution of polypropylene in xylene (0.7-20% by weight of polypropylene) and frequencies in the range 20-1,000 Hz. Our best results in growing fibers were obtained in dilute solutions (1.7-2.4% polypropylene) at the low end of the frequency range (80-110 Hz). Scanning electron microscopy was employed to discern the fibers which had an average diameter of 1 μm. These results are consistent with those obtained by Keller and Jenkins at the Hughes laboratories.

Having shown our system to work successfully with polypropylene, we attempted to grow biodegradable PGA fibers. PGA was dissolved in hexafluoroacetone sesquihydrate to produce a viscous solution even at concentrations as low as 2.3% of PGA. Sonic agitation gave a slight growth of fibrous material before the agitation device failed due to the increased power input necessary to agitate the viscous solution.

We replaced the agitation device and continued our fiber-growth experiments. We agitated PGA solutions under isothermal conditions and during a slow temperature decrease. No fiber formation was noted in any of the solutions. At this point, we were uncertain as to whether the problem was due to the nature of the polymer or to our experimental procedure.

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We subsequently arranged a meeting with researchers from Hughes at our facilities, to discuss technology and methods. Although the discussion with Hughes did not solve our immediate problem, it did give us more insight into the experimental considerations of 3-D fiber production. Hughes agreed to provide us with samples of polypropylene 3-D fibers to determine whether the incorporation of these high-strength and high-modulus fibers into PLA would yield the desired reinforcement. If these fibers provide satisfactory reinforcement, then we will place added emphasis on producing the biodegradable 3-D fibers from PGA or L-PLA.

Based upon our discussion with Hughes, we suspect that higher-molecular-weight samples of PGA than those in our first trails should be used for fiber growth. In addition, we believe that a dilute, low-viscosity solution may be more desirable for achieving the agitation necessary for fiber formation. With this procedure, fiber growth may be propagated by the continued addition of PGA to the mother solution as it becomes depleted during fiber formation. Also, the levels of agitation we obtained with our audio-speaker apparatus may be insufficient for imparting the energy needed for fiber formation. We would need a mechanical shaker head capable of larger displacement amplitudes (0.25 in.) for future fiber-growth experiments.

A comparison of scanning electron micrographs (SEMs) of PGA fibers produced in our laboratory with those produced in early sonic growth attempts by Hughes showed striking similarities. We find these results particularly encouraging, and we believe that with the proper experimental set-up and optimization of experimental conditions, sonic growth of PGA or PLA fibers is possible.

B. Orientation of Biodegradable Polymer Laminates

We anticipated that orientation of non-reinforced polymer plates might serve to improve flexural properties. Orientation is achieved by a drawing process which aligns molecular chains of the polymer. The stretched molecular chains form regular patterns and exhibit increased rigidity due to a more ordered and crystalline structure.

Drawing of the polymer plates was performed on an Instron. Two infrared lamps were used for heat sources with the draw temperature being controlled by the distance of the sample from the heat lamps. The sample of PLA was prepared by the same spin-casting process as described previously. The sample of L-PLA was prepared in the same manner, except a 200-mL sample of the polymer in chloroform was used in the casting process, and a slightly higher pressure (5,000 psi) and a longer press time (1 h) were used in the lamination process.

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Epoxy resin was applied to both sides of the laminate ends to provide a gripping surface. The sample was placed in the Instron clamps, heat was applied, and the sample was pulled in a longitudinal direction at a speed of 0.05 in./min. Samples were stretched 2 to 5 times their original length and cooled while being held in the elongated position. The sample was then cut to the proper size, and the standard flexural tests were performed. The results are shown in Tables XIII and XIV.

In all cases, orientation increased flexural modulus. However, the increase is not dependent on either temperature or draw ratio alone, but a combination of the two. At high temperatures, the polymer actually flows while being drawn, and little orientation is achieved. At low temperatures, the sample simply breaks rather than stretches. At an optimum draw temperature near the glass-transition point, it appears that both flexural strength and flexural modulus increase as the degree of stretch is increased.

A greater change in flexural properties, particularly in modulus of elasticity, was noted for the L-PLA compared to the PLA. This result was not unexpected considering the more steroregular structure of L-PLA, and hence, its enhanced ability to fit into a crystal lattice. The greater crystallinity of L-PLA is reflected in the lamination process. Films of L-PLA do not adhere to each other readily even at elevated temperature and pressure, and in both the orientation process and the Instron testing, delamination was a problem. A better method than lamination for preparing thick samples of L-PLA for orientation could solve this problem and yield oriented samples with higher flexural properties.

C. Injection Molding of Poly(L-Lactide)

We found it difficult to properly laminate L-PLA, a more crystalline form of the lactic acid polymer. As a result, we examined injection molding as an alternative. We anticipated that injection molding of this polymer might provide better reproducibility, easier fabrication, and faster manufacture of polymeric bone plates. Also, a more uniform, homogeneous sample would possibly be obtained.

We had attempted injection molding of PLA initially at the start of the project and rejected it due to problems with polymer hydrolysis. PLA is prepared by a ring-opening polymerization, and the presence of small amounts of moisture at the elevated injection-molding temperature caused severe molecular breakdown of the polyester structure. As a result, the molecular weight of the injection-molded PLA decreased to values unsuitable for implants. An obvious alternative would be the use of a much higher-molecular-weight sample initially, such that the decrease in molecular weight by the injection-molding procedure would still give a satisfactory level. This goal is more readily achieved

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TABLE XIII.   ORIENTATION OF L-PLA LAMINATES

Temperature, °C	Draw Ratio	$\bar{S}$,[a] $\times 10^3$ psi	$\bar{E}$,[a] $\times 10^9$ psi
---	---	2.56	0.02
110	2.0	4.29	0.34
150	2.0	1.79	0.11

a. See Table II for explanation.

TABLE XIV.   ORIENTATION OF DL-PLA LAMINATES

Temperature, °C	Draw Ratio	$\bar{S}$,[a] $\times 10^3$ psi	$\bar{E}$,[a] $\times 10^3$ psi
--	---	2.75	0.16
60	2.7	6.03	0.20
60	4.7	7.42	0.33

a. See Table II for explanation.

with L-PLA than PLA, since high-molecular-weight samples of L-PLA are easier to produce.

In the injection molding of L-PLA, we used a sample with a viscosity of 1.5 dL/g. Fabrication was accomplished with a Frohring Mini Jector Model 45 adjusted to provide a ram pressure of 70 psi. Due to the large size of the injector barrel, a large quantity of material was required to produce the few samples needed. L-PLA has a melting point of 185 ± 5°C, so a higher temperature was selected for the extruder. Since strain lines were evident in the sample molded at 205°C, the temperature was increased to 210°C. The sample at 210°C was clean and strong although somewhat brittle due to the crystalline nature of L-PLA.

We tested both samples in the standard flexural test, and the results of these tests as well as the final inherent vis-cosities are shown in Table XV. These data indicate several important facts. Both the flexural strength and the flexural modulus values were increased by approximately 100% over laminat-ed, unreinforced samples of PLA. As expected, the inherent viscosity of the polymer dropped as the molding temperature was raised, but the molecular weight of the molded polymer was still adequate for a long implant life time (in excess of 1 year). Of course, the degradation time can be shortened, by the use of low-molecular-weight L-PLA, or the use of a copolymer contain-ing glycolide.

TABLE XV.   PROPERTIES OF INJECTION-MOLDED
L-PLA PLATES

Temperature, °C	$\bar{S}$, psi	$\bar{E}$, psi	IV, dL/g in $CHCl_3$
205	8,900	302,600	1.2
210	11,400	398,700	1.1

We suspected that the improvement in flexural properties of the L-PLA plates over those of the PLA plates was due to the crystallinity of L-PLA compared to the amorphous DL-polymer and to the homogeneity of the molded sample. Therefore, we investigated two methods for achieving more homogeneous injection-molded specimens that were free of stress lines. These were higher injection-molding temperature and annealing of the molded sample.

Two samples of L-PLA with different molecular weights were injection molded. One sample had an inherent viscosity of 1.00 dL/g, and the other had an inherent viscosity of 0.60 dL/g, both in chloroform solution. Quantitites of the two polymers were injection molded with a ram pressure of 70 psi at 230, 245, and 260°C. The molded samples were then broken in the

standard flexural tests. The results are shown in Table XVI and Figures 9 and 10.

Data from these trials indicate that the fabrication and flexural properties of injection-molded L-PLA are largely dependent upon temperature and polymer molecular weight. The polymer flows more easily at higher temperatures, and hence forms a plate with fewer strain lines. At very high temperatures, degradation of ester linkages in the polymer becomes a problem with a resultant loss in molecular weight. Mechanical properties increase with molding temperature until degradation phenomena become dominant. As the figures show, once a low value of polymer molecular weight (low inherent viscosity) is obtained by injection molding, the flexural properties decrease. As expected, polymers with lower initial molecular weight reach the break point earlier than those with higher molecular weight. Consequently, the initial molecular weight of the injection-molded polymer is critical. The figures show the flexural properties values for the L-PLA samples with inherent viscosities of 1.00 dL/g increase with molding temperature until typical values for these polymers are obtained. However, the values of flexural strength even at the higher molding temperature are less than those we noted in plates prepared from L-PLA with an initial polymer viscosity of 1.5 dL/g.

Based upon the results of the injection-molding trials, we expected that L-PLA with initial viscosity values in the 1.5-2.5 dL/g range would yield samples with high flexural strength if molded at temperatures in the 260-280°C range.

We subsequently prepared a batch of L-PLA of high molecular weight (IV = 2.41 dL/g) and fabricated plates from the material by injection molding. We experimented with molding temperatures ranging from 250 to 300°C, but we were unable to fabricate suitable samples by this procedure.

At lower temperatures, we did not achieve adequate flow through the injector barrel. At 300°C, the polymer flowed like a low-viscosity liquid. We examined the molded polymer and found that the viscosity had dropped to 0.50 dL/g: thus, the polymer is highly unstable at elevated temperatures with even trace amounts of moisture present. As a result of these experiments, we do not feel that fixation plates with sufficient rigidity and flexural strength can be achieved by injection molding unless complex and impractical equipment modifications are made, and we plan no further work in this area.

D. Reinforcement of PLA Plates with Hydroxylapatite

We suspected that the addition of hydroxylapatite as a filler material could provide reinforcement to polymer plates prepared by the injection-molding process. Hydroxylapatite is a bio-degradable ceramic and is present in bone. In bone, there is an equilibrium between the crystalline and the amorphous form (ACP) of hydroxylapatite. To obtain the ceramic material, we first prepared calcium phosphate by the following procedure

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TABLE XVI. PROPERTIES OF L-PLA PLATES INJECTION MOLDED
AT HIGHER TEMPERATURES

Molding Temperature, °C	$\bar{S}$,[a] $\times 10^3$ psi	$\bar{E}$,[a] $\times 10^3$ psi	Initial IV[b] dL/g	Final IV dL/g
230	1.55	0.244	1.00	0.79
245	2.51	0.328	1.00	0.64
260	4.90	0.379	1.00	0.56
230	1.06	0.178	0.60	0.48
245	1.94	0.213	0.60	0.40
260	0.69	0.134	0.60	0.23

a. See Table II for explanation.

b. See Table VIII for explanation.
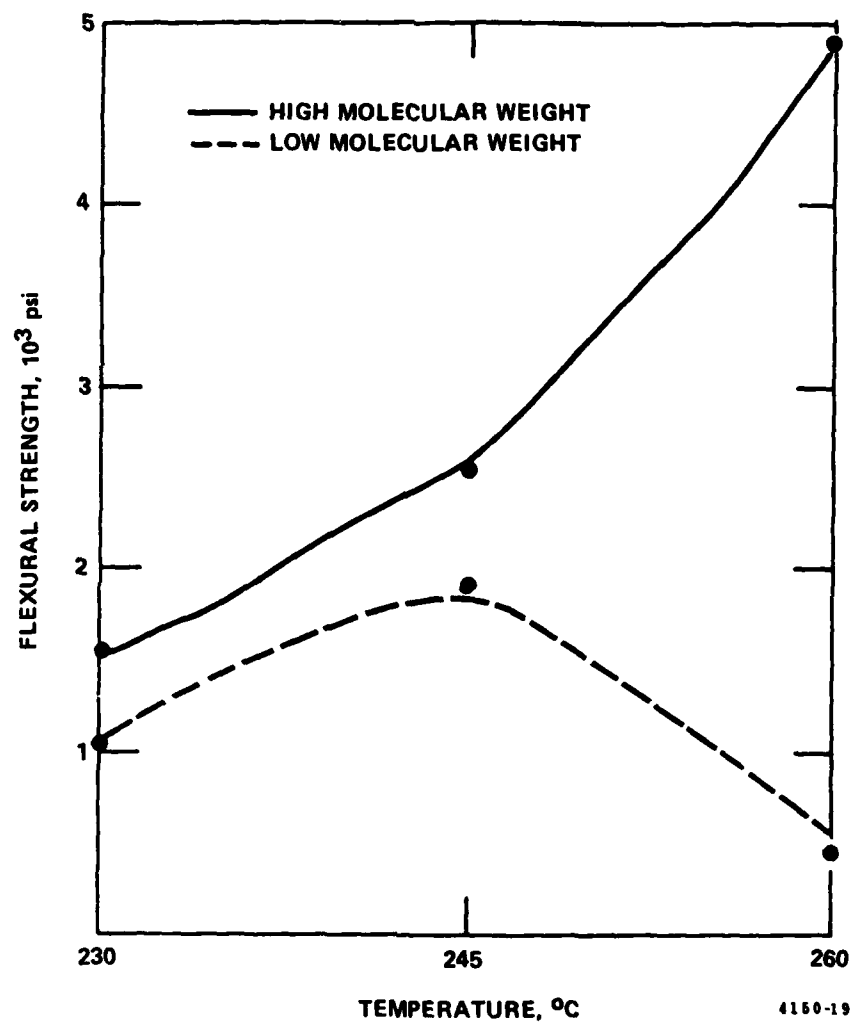
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Figure 9. Effect of injection-molding temperature on flexural strength of L-PLA plates.
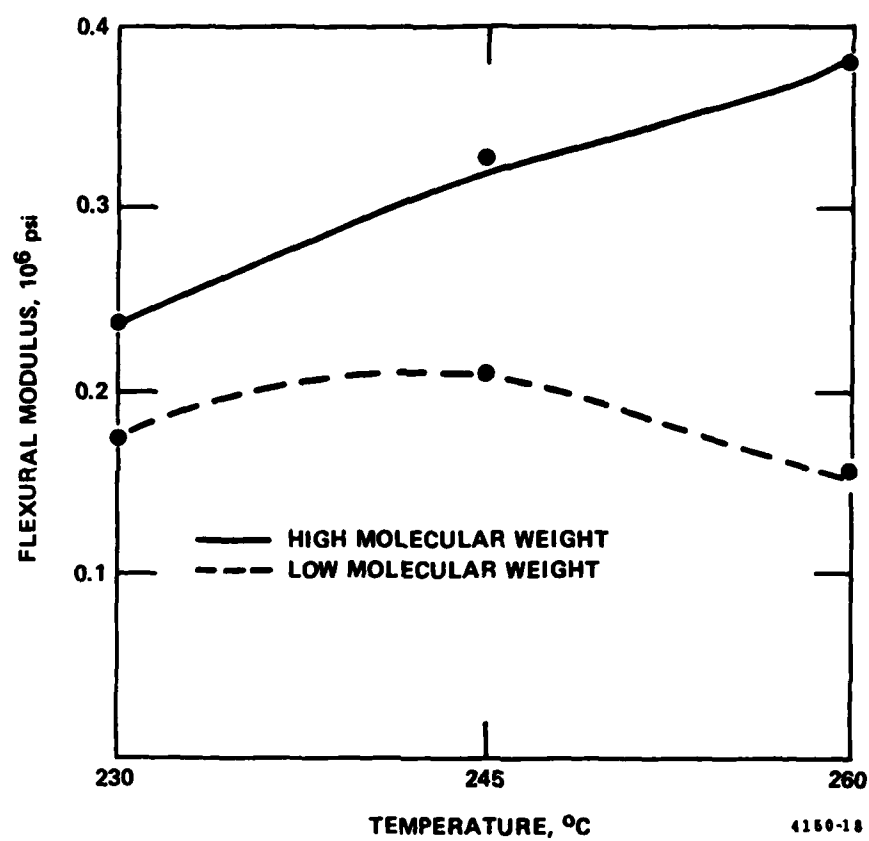
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Figure 10. Effect of injection-molding temperature on flexural modulus of L-PLA plates.

from Jorcho et al. [Journal of Material Sciences 11, 2027-35 (1976)]. Solutions of calcium nitrate (1.00 M) and dipotassium hydrogen phosphate (0.60 M) were prepared. The pH of 90 mL of the calcium nitrate solution was adjusted to 11.5 with concentrated ammonium hydroxide, and the solution was diluted to 180 mL. Similarly, the pH of 150 mL of the dipotassium hydrogen phosphate was adjusted to 11.5, and the resultant solution was diluted to 320 mL. The calcium solution was stirred vigorously and the phosphate solution was added dropwise over a period of one hour. The resulting mixture was then boiled for one hour. After cooling, it was centrifuged, and the slurry was filtered on a Buchner funnel for two hours with mild suction and a rubber dam. The filter cake was then dried at 90°C for 15 hours.

The hard cake that resulted was cracked into pellets and sintered at 1000°C for one hour. SEM showed an amorphous product at 7,000X magnification.

A 50% mixture of the ACP and L-PLA (IV = 1.5 dL/g) was prepared. The mixture was injection molded by the same procedure as that described above for L-PLA. The product showed a homogenous dispersion of the ACP within the polymer; however, the results of standard flexural tests showed no reinforcement by the hydroxylapatite powder. These poor results are probably due to the amorphous form and low aspect ratio of the hydroxylapatite prepared by this procedure. We expect that the reinforceement would be much greater for a high aspect and crystalline form of the ceramic material.

We attempted to grow hydroxylapatite crystals from a mother liquor, and we tried to reinforce PLA with these crystals. In glassware rinsed with hydrochloric acid, we prepared 2 mM solutions of calcium phosphate, $Ca_{10}(PO_4)_6(OH)_2$ (tribasic powder, Baker) in deionized water. The pH of the solution was adjusted to 7.4 with 0.1 N NaOH. At 2-week intervals, the slurry was examined by SEM for crystal growth, and crystals were removed and incorporated into L-PLA composites. None of the materials formulated in this fashion provided composites with acceptable property levels.

In an attempt to produce a hydroxylapatite ceramic product suitable for plate reinforcement, we incorporated ACP into a number of binders and then sintered the materials. During the sintering process, grains recrystallized to form larger grains, with coalesence occuring at intersecting grain boundaries. The grain-growth process is governed by boundary-energy considerations.

One of the bonding systems we employed was ACP mixed with hydroxyethyl cellulose (HEC) and HCl. A solution of ACP in HCl was prepared (25% by weight ACP), and hydroxyethyl cellulose was slowly added to the solution with vigorous stirring. Agitation was continued until a viscous slurry comprising 22% by weight ACP resulted. The slurry was then coagulated in an

acetone bath. Another binder system that we employed was stearic acid. ACP was mixed with stearic acid to give a blend containing 80% by weight ACP. The powder was then pressed between flat plates at 30,000 psi and 200°C. A plate of 100% ACP was also prepared under identical pressing conditions.

We sintered all samples by heating them slowly from ambient temperature to 1150°C over a period of 5.5 hours. This temperature was held for one hour, and the samples were allowed to cool overnight. The pressed plates formed relatively brittle materials. The other samples formed weak films filled with many voids and crevices. Thermal fracture, which occurred during the processing of all samples, prevented the fabrication of sections sufficiently large for tensile testing.

We next investigated a number of different preparations and firing schedules in an attempt to produce hydroxylapatite materials of a quality acceptable for use as reinforcing materials.

Initially, we prepared ceramics by the method of Kato et al. [Biomat., Med. Div., Art. Org., 7(2), 291-297 (1979)]. The apatite powder was prepared by the heating of intimate mixtures of calcium phosphate and calcium hydroxide. The mixtures were maintained at 900°C for 16 hours. Samples comprising 10, 30, and 50% by weight of calcium hydroxide were prepared in this fashion. After firing the powder mixtures, we allowed them to cool to room temperature, and then we cold pressed them into 0.20-cm diameter columns in a steel mold at a pressure of 1000 kg/cm^2. The pressed columns were subsequently heated at 1125°C for two hours under atmospheric pressure. Columns containing 10 and 30% weight of calcium hydroxide cracked upon removal from the firing oven. Columns containing 10 and 30% by weight of calcium hydroxide were less brittle.

We prepared additional ceramic mixtures by the same procedure, and we fired them by placing them in an oven initially at room temperature and increasing the temperature by 300°C each hour until a temperature of 1150°C was obtained. The samples were held at this temperature for 16 hours. The oven was turned off, and the samples were permitted to cool in the oven to room temperature. The samples containing 10% by weight of calcium hydroxide was soft. The samples with 30 and 50% by weight of calcium hydroxide, however, were harder than the samples we obtained from the previous firing schedule.

We also attempted to sinter calcium phosphate powder with hydroxyethylcellulose (HEC) as a binding agent. Both HEC solution (50% in H$_2$O) and dry HEC powder were used. One sample was prepared containing 50% by weight of dry HEC powder. Both mixtures were hand pressed into alumina crucibles and fired according to the following schedule:

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Firing Time, h	Firing Temperature, °C
1	205
5	430
2	650
9	870
9	1150

At the end of the firing schedule, the oven was turned off and the samples were allowed to cool slowly, in the oven, to room temperature. The sample containing HEC solution appeared to be more resistant to fracturing or abrasion than the sample containing dry HEC powder.

We prepared additional samples of calcium phosphate powder with HEC binder and fired them by placing them in an oven initially at room temperature and increasing the temperature by 300°C each hour until a temperature of 1150°C was reached. The oven was maintained at this temperature for 16 hours. The oven was turned off, and the samples were allowed to cool to room temperature in the oven. With this procedure the samples containing 50% (by weight) of dry HEC were fairly hard, whereas the samples prepared with HEC solution were soft and crumbled under hand pressure.

The ceramics prepared by the procedures described above were of generally poor quality and would be unacceptable as a fixation-plate reinforcement material. The principal difficulties encountered during the preparation of calcium phosphate ceramics are achievement of high strength and single-phase compositional integrity. A variety of ceramic forms of hydroxylapatite $[Ca_{10}(PO_4)_6(OH)_2]$ and β-tricalcium phosphate $[Ca_3(PO_4)_2$; whitlockite] have been reported in the literature. Although we have no X-ray diffraction data at this time, we believe that the poor quality of the ceramics produced by our current techniques is a result of the presence of multiple phases in the final sintered product. For this reason, we turned our attention to the production of a high-strength pure β-whitlockite ceramic. β-Whitlockite is bioresorbable, while some ceramic forms of hydroxylapatite are not.

We prepared green states which should yield 100% of β-whitlockite ceramics by the precipitation procedure of Salsbury and Doremus [Journal of Materials Science 14, 142-150 (1979)]. The method of precipitation was similar to the method used for precipitation of hydroxylapatite. The procedure was as follows:

A solution of $Ca(NO_3)_2$ (1.40 mol) in 900 mL of deionized water was brought to pH 11 with concentrated NH_4OH and then diluted to 1800 mL with additional water. A solution of $(NH_4)_2HPO_4$ (1.00 mol) in 1500 mL of deionized water was brought to pH 11 with concentrated NH_4OH and diluted to 3200 mL to dissolve the resulting precipitate. The pH was checked and additional concentrated NH_4OH was added if necessary to ensure a pH of 11.

The calcium solution was vigorously stirred at room temperature, and the phosphate solution was added dropwise to produce a milky, somewhat gelatinous precipitate which was then stirred overnight (in excess of 16 hours). The mixture was then centrifuged, and the clear supernatant was decanted. The resulting mineral sludge was homogeneously resuspended in deionized water and served as a feedstock.

To produce green states which should ultimately afford 100% β-whitlockite ceramics, aliquots of the feedstock suspension were recentrifuged, homogeneously suspended into two volumes of aqueous $(NH_4)_2SO_4$ (1% solution), and filtered on a Buchner funnel with application of mild suction and a rubber dam. After filtration for several hours, the compact clay-like cake was dried intact at 90°C overnight to produce directly the green state.

The green cake was ground into a powder with a mortar and pestle and packed into alumina crucibles. The samples were placed in the oven and heated to 600°C over a 0.5-hour period. The temperature was then raised quickly to 1150°C, and the samples were sintered isothermally for 1 hour, followed by a soak at 900°C for 4 hours.

Materials prepared in this fashion were much harder than the materials prepared by any previous procedure. We are currently in the process of fabricating plates and rods for evaluation as reinforcement materials. We also plan to investigate the production of continuous fibers of β-whitlockite. The fibers would be used to reinforce the PLA plates in the same fashion as we demonstrated for commercial, non-bioabsorbable carbon and ceramic fibers.

E. Crosslinking of PLA

As an alternative to composite fabrication, we examined crosslinking of PLA as a method of enhancing stiffness and rigidity. In general, polymeric materials with high flexural strengths and high flexural moduli may be obtained by chemical crosslinking of polymer chains. Crosslinking reduces polymer mobility by covalently bonding subunits of different polymer

chains. Decreasing chain mobility reduces the extent to which
a material may relieve imposed stresses by deformation and in
many cases alters the failure mechanism from plastic yield and
deformation to brittle fracture at high load levels. In
addition to the desired increase in load at failure, it is
also necessary with crosslinked polylactide used as bone plates
that the crosslink bonds be subject to biodegradation to harmless
end products. With this in mind, we investigated several methods
of crosslinking PLA.

One of the first methods that we explored was the addition
of a trifunctional molecule to the system. We chose glycerol as
a likely candidate, since all three hydroxyl groups may be subject
to attack by the ring-opened dimer of lactide. The polymerization
was conducted in a manner similar to the polymerization of
L-lactide described previously. L-Lactide (49 g), tetraphenyl
tin (0.032 g), and glycerol (2.25 g) were placed in oven-dried
glassware. The mixture was heated at 170°C with stirring
for 5.5 hours. We observed no change in viscosity and only a
slight darkening of the solution. After an additional 17.5 hours
of heating, we cooled the vessel to facilitate handling, and then
we added 1 drop of lauryl alcohol as a chain initiator. After
an additional heating of the mixture for 23 hours produced no
change, we cooled the solution to obtain a hard, brittle, amber-
colored polymer which was readily soluble in dichloromethane.
This solubility behavior was indicative of a low-molecular-weight,
uncrosslinked product. Apparently, glycerol did not react with
the PLA polymer chains to provide crosslinking. In fact, gly-
cerol appeared to act as a chain terminator, and thus hindered
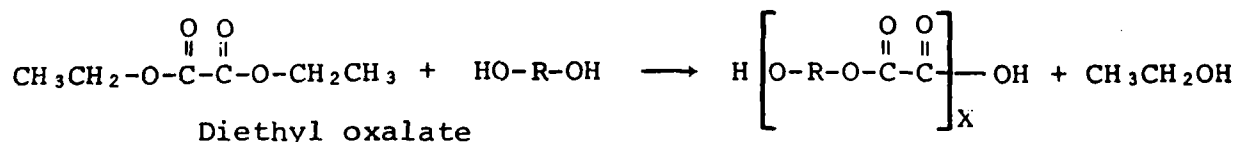the polymerization.

We continued our efforts at crosslinking PLA by introducing
glycerol after a prepolymer had been formed. We also attempted
to prepare a PLA prepolymer with glycerol end groups and crosslink
it with a diisocyanate; however, these methods were not successful
in producing a crosslinked polymer.

As an alternative approach, we added maleic anhydride to
a PLA polymerization at the prepolymer stage with the expectation
that it would incorporate unsaturated sites into the PLA. We
then tried to crosslink this PLA through the unsaturated groups
in the presence of other vinyl monomers such as ethylene glycol
dimethacrylate and a small amount of methyl methacrylate. The
resulting polymer had a lower viscosity than standard PLA,
indicating that maleic anhydride may have resulted in chain
termination. We subsequently added ethylene glycol dimethacrylate
and methylmethacrylate with a peroxide catalyst to a portion
of the polymer and continued heating for 7.5 hours. The resulting
polymer dissolved in dichloromethane but would not precipitate
in methanol, an indication of a low-molecular-weight material.
Apparently no crosslinking had occurred.

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The results of all of our experiments with PLA indicated that the introduction of crosslinking moieties into the polymer chain would be difficult, and we diverted our efforts to biodegradable polymers prepared by a different polymerization mechanism.

F. Synthesis and Attempted Crosslinking of Copolyoxalates

The lack of success in crosslinking poly(DL-lactide) prompted us to examine other biodegradable resins as possible bone-plate materials. Isomorphic copolyoxalates have been recently patented (U.S. Patent 4,141,087) by Ethicon, Inc. as synthetic absorbable suture materials. The polymerization of the copoly-oxalates proceeds by a transesterification reaction and holds greater promise for the incorporation of a trifunctional, cross-linking molecule than does the ring-opening polymerization of polylactide. Highly crystalline isomorphic polyoxalate polymers may be prepared as shown below by reacting mixtures of cyclic and linear diols with dialkyl oxalate, preferably in the presence of an inorganic or organometallic catalyst.

$$CH_3CH_2-O-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-O-CH_2CH_3 \; + \; HO-R-OH \; \longrightarrow \; H\left[O-R-O-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}\right]_x OH \; + \; CH_3CH_2OH$$

Diethyl oxalate

where $R = -(CH_2)_6-$ [1,6-hexanediol]

or $-CH_2-\bigcirc-CH_2-$ [1,4-cyclohexanedimethanol]

For our initial studies with these materials, we prepared 95/5 poly(trans-1,4-cyclohexylenedicarbinyl-co-hexamethylene oxalate) by the following procedure:

Distilled diethyl oxalate (50.0 g, 0.342 mol), trans-1,4-cyclohexanedimethanol (51.5 g, 0.357 mol), 1,6-hexanediol (2.2 g, 0.019 mol), and stannous octoate (0.33 $\underline{M}$ in toluene, 0.3 mL) were added to a 200-mL, three-neck, round-bottom flask equipped with a mechanical stirrer. The addition of all materials was carried out under nitrogen purge. The prepolymer was formed by heating the mixture at 120°C for three hours under nitrogen at one atmosphere while allowing the formed ethanol to distill. This step was followed by heating the contents 160°C for two hours. The prepolymer was then allowed to cool overnight.

The prepolymer was reheated in vacuo at 220°C for
7 hours. After the initial melting, the prepolymer
became darker in color, and more ethanol was given
off. At the end of the 7 hours of heating, the
polymer was allowed to cool to room temperature.
The viscosity of the final product was 0.21 dL/g
as measured in chloroform.

We attempted to increase the molecular weight of the product
by reheating it at an elevated temperature. Twenty-five grams
of the polymer was placed in a 200-mL, three-neck flask and
heated at 180°C for 22 hours under vacuum (0.3 mm Hg).
The final product was insoluble in chloroform, and we suspect
that the insolubility is a result of crystallinity and high
molecular weight.

We also attempted to crosslink a portion of the prepolymer.
Twenty-five grams of polymer was placed in a small, three-neck
flask with 0.2 mL of glycerol. The mixture was stirred at
for 22 hours under a vacuum of 0.3 mm Hg. Again the product
was insoluble in chloroform.

We believe the copolyoxalate materials, by virtue of
their high crystallinity and potential crosslinking ability through
transesterification, offer significant promise as potential bio-
degradable fixation plate materials. Our current efforts are
directed toward the crosslinking of these polymers by the sub-
stitution of unsaturated diols into the polymer and crosslinking
through the double bond of these molecules.

VIII. CONCLUSIONS AND RECOMMENDATIONS

In the last two years of Contract DAMD17-78-C-8059, "Development of Biodegradable Implants for Use in Maxillofacial Surgery," we have identified a number of viable approaches for developing high-strength resorbable implant materials. Several modifications to the fabrication process which we originally proposed as being potentially successful for the production of high quality fixation plates were evaluated and eliminated.

During the first year of the contract, we investigated the injection molding of PLA samples, but we found this approach unacceptable because of the dramatic decrease in material properties during fabrication. Polylactide, like other polyesters, is susceptible to hydrolysis in the presence of moisture and heat. Injection molding of PLA without elaborate precautions to exclude all traces of moisture leads to rapid deterioration in molecular weight with a subsequent loss in physical-mechanical properties. We subsequently developed methods for fabricating laminated samples from biodegradable polymer films. The samples prepared in this manner showed no significant change in molecular weight as a result of processing. The process, however, did not lend itself to fabrication of plates from L-PLA. The L-PLA material is more crystalline and film samples were prone to brittle fracture. As a result of these problems, we re-examined injection molding for producing plates of this polymer. Based on our experience with the PLA material, we began the fabrication with high-molecular-weight material to compensate for the probable deleterious effects of injection molding. L-PLA, like the amorphous PLA polymer, exhibited a marked reduction in viscosity and mechanical properties, and we were unable to produce samples with sufficient strength and rigidity for use in the production of fracture fixation plates.

We also attempted to orient PLA samples to improve flexural properties. Orientation is achieved by a drawing process which aligns molecular chains of the polymer. The stretched molecular chains form regular patterns and exhibit increased rigidity due to a more ordered and crystalline structure. The orientation process was found to be insufficient for producing fixation plates of adequate quality.

We reinforced plates of PLA with both commercially available carbon and ceramic fibers. These materials were fabricated to demonstrate the merit of a fiber-reinforced system. The samples prepared in this fashion exhibited flexural properties within the selected target range for fracture fixation materials. Samples of these materials were provided to the Army in August 1980 for an implant study in dogs. The results of the study were favorable, with the dogs healing without complication. We found from in vitro studies that the plates retained adequate strength and rigidity for 4-6 weeks. This result, coupled with the results of the canine study, suggests that the target values of flexural modulus and flexural strength may be higher than

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necessary, and that suitable fixation plate devices may be
fabricated from materials with lower values for these proper-
ties.

The materials used in this model study were not, however,
totally biodegradable. We investigated a number of alternative
methods for producing a totally biodegradable fixation plate
system. We examined the utility of commercially available
PGA sutures as reinforcing fibers, but we found that, even
when fully drawn, these fibers still did not exhibit the
character required when incorporated into a biodegradable
PLA plate. We also attempted to grow 3-D PGA fiber networks
for reinforcement by a sonic-agitation process. We were unable
to produce satisfactory fiber networks by our current technology.

We attempted to crosslink PLA by a variety of methods, but
none were successful. We believe that the difficulty with
crosslinking PLA lies, to a greater extent, in its ring-opening
polymerization mechanism. Copolyoxalate materials were investi-
gated as an alternative, and we believe that we are close to
achieving a crosslinkable system with these polymers at this
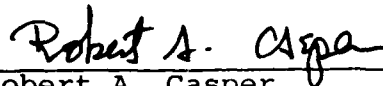time.

Our successful reinforcement of PLA with commercially
available ceramic fibers led us to the investigation of bio-
degradable ceramic reinforcing systems. We investigated hydroxyl-
apatite powder as a reinforcing filler, but we found no
substantial improvement in plate flexural properties. We
have, however, been successful in optimizing green-cake composi-
tion and firing schedule to produce a sintered hydroxylapatite
ceramic that is hard and dense. We are now attempting to
fabricate this material into rod, plate, and fiber form for use
as reinforcement materials.

Both crosslinked copolyoxalate systems and hydroxylapatite
ceramic reinforcement offer significant promise for providing
totally biodegradable fixation plates suitable for fracture
repair. Further research and optimization studies on these
approaches should yield biodegradable systems acceptable for
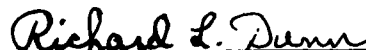maxillofacial implantation.

IX. ACKNOWLEDGEMENTS

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